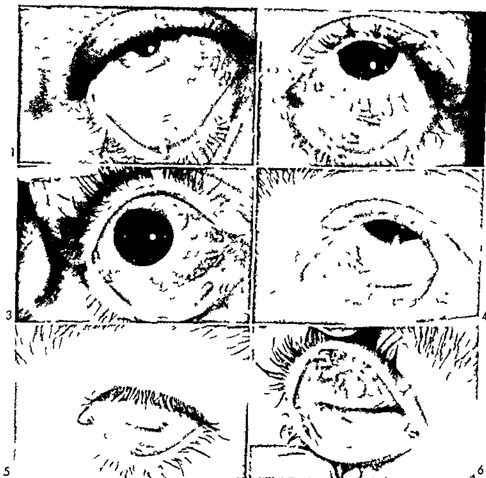


PLATE I

FIG 1 Acute atopic conjunctivitis due to ragweed hay fever
FIG 2 Acute atopic conjunctivitis due to strawberries
FIG 3 Acute atopic conjunctivitis due to crab meat
FIG 4 Chronic atopic conjunctivitis cause undetermined Conjunctival n ino
[illegible] Alleviated by corticosteroids

OCULAR ALLERGY

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Ocular Allergy

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THE WILLIAMS & WILKINS COMPANY

Baltimore · 1958



Library of Congress
Catalog Card Number
58 8598

Printed and Composed at the
Waverly Press Inc
Baltimore 2, Md U S A

To J. S. T. and C. S. S.

PREFACE

In ophthalmology, perhaps more than in any other specialty, allergy in the past decades has come to be accepted as a major etiologic mechanism. An increasing number of apparently unrelated ocular affections are now best explained on the basis of hypersensitivity. This is not surprising in view of the fact that the eye and its adnexae offer a unique opportunity to observe and study, both clinically and experimentally, all the fundamental allergic reactions to an extent not possible elsewhere in the body. Unfortunately, however, because ocular allergies often resemble inflammations of nonallergic origin, on many occasions allergy is not recognized when it is present, or is erroneously diagnosed when it does not exist.

It was felt by the authors that the time was propitious for reappraisal of the subject of ocular allergy. No such book has been written in the twenty-five years since Dr. Alan C. Woods presented his excellent monograph on the subject. During this period our knowledge and appreciation of allergy has grown tremendously.

This book attempts to correlate and classify the clinical manifestations of ocular allergy in accordance with the various allergic mechanisms involved. Our consideration of the subject has been tempered and disciplined by our studies and experience in the related fields of ocular microbiology, external diseases and therapeutics. Utilizing accepted allergic principles, we have been able to interpret ocular hypersensitivities, with only few exceptions, within the basic categories of anaphylactic, atopic, microbial and contact reactions. Through such a practical organized approach we feel that the clinician will be better equipped to recognize and evaluate the many forms which ocular allergies assume, and to resolve many other troublesome therapeutic problems arising from the fact that different allergic responses require different types of treatment.

We trust that this book will prove useful in the clinical practice of many physicians, not only ophthalmologists and allergists, but also those engaged in allied specialties such as dermatology and industrial medicine. In addition, it is felt that this volume contains information of value to the cosmetic and pharmaceutical industries not readily available elsewhere.

In order to provide the reader with a useful source of reference to the many phenomena encompassed by ocular allergy, every effort was made to evaluate the entire world literature, both old and new. It is interesting that in certain instances, original sources, when restudied for historical as well as other reasons, proved, in the light of modern clinical knowledge

to be of more basic significance than could possibly have been appreciated at the time they were published

Because of the difficulties inherent in the translation of color transparencies to black and white illustrations Mr Robert W Carlin utilized electronic methods for the preparation of prints To our knowledge this is the first time that this procedure has been done All illustrations unless specifically acknowledged are from our own clinical collection Special appreciation is extended to Doctors E Sidi and E Mawas of Paris to the Department of Dermatology and Syphilology of the New York University Post Graduate Medical School (Dr Marion B Sulzberger Chairman) and the Skin and Cancer Unit of the New York University Hospital and to Dr Harvey E Thorpe for their kindness in permitting us to use their photographs In addition we wish to thank all others who have allowed us to reproduce their illustrations

The authors also wish to thank the editors of the *Journal of the American Medical Association* the *American Journal of Ophthalmology* the *Transactions of the American Academy of Ophthalmology and Otolaryngology* the *Eye Ear Nose and Throat Monthly* and *Oral Surgery Oral Medicine and Oral Pathology* for permission to use material previously published by us in these journals The assistance of Mr Robert R Feinstein and Miss Florence E Wall in the preparation of certain chapters was most valuable We are deeply indebted to Mr Edward Sagarin for the great deal of material he has supplied us his editorial advice and his pain taking preparation of the index Lastly we wish to thank Mrs Mae Margadona and Miss Esther Glanzspiegel for the careful preparation of the manuscript

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1

BASIC PRINCIPLES OF ALLERGY

William B. Sherman, M.D.

THE CONCEPT OF ALLERGY

In the early studies of immunity it was occasionally observed that exposure to infective and toxic agents rendered persons or animals more reactive rather than less reactive or immune. For example, when vaccination against smallpox was repeated on the same person, the second inoculation produced an accelerated reaction. Patients with tuberculosis were found to react strongly to tuberculin, a filtrate of the tubercle bacillus which was harmless to those not infected, indicating that exposure through infection produced a new type of reactivity. In attempting to immunize dogs to the toxin of the sea anemone, Portier and Richet (1) in 1902 found that animals which showed little or no reaction to the first injection might react violently to a repetition of the same dose. They applied the term anaphylaxis to this phenomenon and considered it an increased susceptibility to the toxin. However, the reaction was subsequently shown to be unrelated to toxicity and was readily produced with egg albumin or horse serum as antigens. At almost the same time, Arthus (2) described the phenomenon of local hypersensitivity to repeated injections of antigen. In 1905 von Pirquet and Schick (3) described the various types of reactions to horse serum observed as a result of the clinical use of diphtheria antitoxin. In the following year von Pirquet (4) proposed the general term *allergy* to denote all of these altered reactions of living organisms to repeated contacts with infectious or antigenic agents.

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Both the concept of specific hypersensitivity and the term allergy have been widely applied in subsequent years. Many other diseases, including hay fever, asthma, eczema, urticaria, contact dermatitis, and drug sensi-

tizations have been included in the classification of allergic reactions A mechanism of sensitization has been suggested as playing a part in the causation of several diseases of unknown etiology such as rheumatic fever periarteritis nodosa and glomerular nephritis In each of these diseases evidence strongly supporting the hypothesis has been offered by clinical and experimental studies Conclusive proof is still lacking but many of the observed features of these diseases are now explained on this basis

ALLERGY AS AN ANTIGEN ANTIBODY REACTION

The original concept of allergy as an altered reaction to infection and antigenic agents carried the implication of an immunologic or antigen antibody basis Allergic reactions showed many of the features of immunologic reactions Allergy like acquired immunity, was an altered reaction of the individual rather than a characteristic of the species Allergic reactions showed the high degree of specificity which is characteristic of immunologic reactions Most types of sensitization obviously resulted from previous contact with the causative agent When the time of the sensitizing contact could be clearly established the period elapsing before sensitization developed was consistent with the usual incubation period of antibody formation Even in such allergies as hay fever which appeared to arise spontaneously after only normal exposure to the allergens in the environment there was negative evidence of the influence of contact in that there was no sensitization to antigens to which the allergic person had never been exposed

With the classical methods of demonstrating antibodies such as the precipitin and complement fixation reactions and the passive sensitization of guinea pigs the presence of antibodies could be demonstrated in only a few types of allergies—namely anaphylaxis, serum sickness and the Arthus reaction The sera of persons with asthma hay fever contact dermatitis and tuberculin sensitization showed no evidence of antibodies when tested by these methods However the presence of antibody activity in the sera of patients with atopic diseases was soon established A sensitizing substance in the blood in asthma was shown by Ramirez (5) who reported the sensitization of a nonallergic person by a transfusion of blood from an asthmatic patient Prausnitz and Kustner (6) demonstrated the presence of the same sensitizing factor by injecting sera of patients with asthma or hay fever into the skin of normal persons to produce a local passive sensitization which could be shown by skin tests at the sites of injection This local reaction is referred to as the *Prausnitz Kustner phenomenon* or as *passive transfer* of sensitization

The substance in the serum producing this passive sensitization while lacking the usual antibody properties of precipitin activity and passive

sensitization of guinea pigs, is considered a *skin-sensitizing antibody* or *reagin*. Aside from its failure to react with antigen in the test tube, this skin-sensitizing antibody differs from other antibodies in several respects. 1) It has a special affinity for skin and mucosa. If injected into the skin, it remains fixed in the site for weeks. When injected intravenously, it is rapidly localized in the skin and mucosa. 2) Unlike most antibodies, including the anaphylactic antibody of guinea pigs, it does not pass through the placenta from mother to child. The child of an atopic mother may inherit the tendency to develop atopy but he is not born passively sensitized to the same antigens which affect the mother. 3) The skin-sensitizing antibody is not limited to the gamma globulin fraction of the serum proteins in which most other antibodies are found. 4) The skin-sensitizing activity is destroyed by heating the serum at 56°C and is not restored by adding complement.

In contact dermatitis and tuberculin sensitization the serum does not transfer sensitivity to normal individuals. Landsteiner and Chase (7) showed that these two types of sensitization in experimental animals could be transferred to normal animals by injecting suspensions of living lymphocytes and monocytic cells from sensitized animals. This type of transfer by cells but not by serum obviously differs from the previously known manifestations of antibody activity. Although the mechanism is not yet entirely clear it is generally considered evidence of the presence of a fixed *cellular antibody*. Thus the employment of new techniques has demonstrated the association of various types of antibodies with an increasing number of allergic reactions.

There are still many conditions which by all clinical criteria may be classed as allergies in which the presence of antibodies has not yet been demonstrated. Notable among these are asthma and urticaria due to infective agents, and most of the drug allergies. From the resemblance of these conditions to known immunologic reactions it appears probable that some antigen antibody mechanism is involved but present methods of study do not permit its demonstration.

Conditions with clinical features resembling those of the reactions of hypersensitivity to antigenic substances have been found to result from nonmaterial influences such as physical agents—light, cold and heat—and bodily or emotional stress. Many authors have included such phenomena in the classification of allergy, considering them broad types of reaction to environmental factors. Such a general application of the concept necessarily includes conditions which differ greatly in their basic mechanisms and has led some authorities, such as Karsner and Rich, to abandon the term allergy as too vague for scientific use. In order that the word may have a precise meaning it seems wisest to limit the term allergy to those

reactions which have a demonstrable antigen antibody basis or which may be reasonably presumed to have such a basis As noted later in this chapter such a mechanism is demonstrable in some cases of allergy to physical agents while others appear to differ in their pathogenesis

ALLERGENS AND ANTIGENS

The substance causing an allergic reaction is called an *allergen* This word is to be distinguished from the word *antigen* which indicates a substance which stimulates the formation of antibodies when it is injected into animals All antigens are capable of acting as allergens as the formation of antibodies in susceptible species of animals induces the anaphylactic type of sensitization On the other hand many substances which are not antigens act as allergens

All antigens are complex biologic materials of high molecular weight most are proteins but a few are complex carbohydrates All natural proteins act as antigens when injected into any species other than that from which they are derived Human sensitization of the anaphylactic type results from injection of foreign proteins most often from prophylactic or therapeutic injections of antisera derived from horses

The allergens causing atopic diseases are in general protein containing organic materials which are capable of acting as true antigens However in atopy they gain access to the body either as inhaled dusts or as ingested foods Prominent among the antigenic dusts which act as inhalants are pollens mold spores animal danders feathers down cosmetics insecticides fertilizers and grain dusts House dust as collected in vacuum cleaners is definitely allergenic and often produces reactions in patients who do not react to any of the fibers feathers etc which obviously contribute to its formation or to the molds and bacteria with which it is contaminated It has been suggested that in the process of disintegration some of these ingredients develop new antigenicity

Essentially all natural foods are potential antigens and may act as allergens in the causation of atopic disease Early in life milk eggs citrus fruits and chocolate seem to be the most common offenders Cereals berries melons nuts tomatoes fish and shellfish are also frequently implicated

In the causation of contact dermatitis proteins and true antigens play an insignificantly small part It is caused by a great variety of substances most of which are rather active chemical compounds both organic and inorganic of relatively simple structure and low molecular weight The lipoids and resins of plants such as poison ivy are important factors Many synthetic dyes chemicals and drugs are factors as are simple salts of metals such as nickel and mercury and many other compounds None

of these is an antigen in the sense of stimulating the formation of typical antibodies when injected into experimental animals It is believed that they act as *haptens* combining with the tissue proteins to form complex antigens the specificity of which is determined by the hapten groups However, in the case of many contact allergens the existence of such a hapten protein compound is hypothetical and its nature unknown

IMMEDIATE AND DELAYED ALLERGIC REACTIONS

Allergic reactions may be divided into two main groups, immediate and delayed reactions (table 1)

In general the immediate reactions are apparent within a few minutes after adequate exposure to the antigen Characteristically, they are associated *with the presence of circulating antibodies in the blood plasma* although these may not be demonstrable in every case These circulating antibodies have the property of inducing passive sensitization to the same antigen in normal individuals of the same species, and often of other species Physiologically these reactions involve principally the blood vessels and smooth muscles of the body Many of the manifestations of the immediate reactions resemble the actions of histamine and may be inhibited to some extent by antihistaminic drugs and epinephrine In most

TABLE 1

Classification of allergic reactions

Type of Reaction	Characteristics	Resulting Conditions
I *Immediate*	A *Anaphylaxis*	
Reactions of smooth muscle and blood vessels	Readily induced	Anaphylactic shock
Histamine a factor	Heredity not a factor	Serum sickness
Associated with antibody	Precipitating and anaphylactic antibodies	Arthus reaction
	B *Atopy*	
	Not easily induced	Hay fever
	Heredity a major factor	Asthma
	No precipitin or anaphylactic antibody	Urticaria
		Infantile eczema
		Atopic dermatitis
II *Delayed*	A *Contact sensitization*	
Cellular reactions	Induced by surface contact	Contact dermatitis
Histamine not a factor	B *Bacterial sensitization*	
No humoral antibody	Induced by infection	Tuberculin allergy
		Histoplasmin allergy
		Trichophytin allergy
		Oidiomycin allergy etc

instances this type of sensitization is manifested by an immediate wheal and erythema response to intracutaneous skin tests with the antigen Patch tests are generally negative

The delayed allergic reactions usually occur twelve to twenty four or more hours after contact with the allergen No circulating antibodies are demonstrable in the blood plasma The sensitization is a property of the cells themselves and is tran mitted to succeeding generations of cells propagated in tissue cultures In certain allergies of this type the lymphoid cells of the sensitized animal have been shown to transfer sensitization to normal animals of the species although the serum or plasma does not induce passive sensitization Since reactions of this type are essentially cellular they can occur in the absence of blood vessels and smooth muscle There is no similarity to the effects of histamine and the reactions are not affected by antihistaminic drugs or epinephrine Reactions to intracutaneous tests with antigen are of the delayed inflammatory type and patch tests are usually positive

Anaphylaxis

Included in the group of immediate reactions are the various manifestations of anaphylaxis and the atopic diseases Anaphylaxis and its variations such as serum sickness and the Arthus reaction are readily induced experimentally in essentially all individuals of susceptible species by adequate exposure to antigen They are usually associated with the presence of typical precipitating antibodies in the serum which also induces passive anaphylaxis in guinea pigs Heredity is a negligible factor in the development of these sensitizations

Atopy

In the atopic diseases such as hay fever bronchial asthma urticaria infantile eczema and atopic dermatitis heredity plays a major part Individuals predisposed by heredity acquire sensitization of this type spontaneously after only natural contact with the allergen On the other hand it is not easy to artificially induce new sensitizations of this type in normal persons or even in those already affected by other allergens

Delayed Allergy

The delayed allergic reactions include allergies of the tuberculin type to infective agents such as bacteria fungi viruses and spirochetes and also contact dermatitis Within this group al o there are differences in the mode of development of sensitization The delayed allergies to infectious agents u ually develop only as a re ult of infection by the living agent or by injection of the dead microbe with suitable adjuvants The soluble anti

gens such as tuberculin which serve to elicit the skin reaction do not in general induce sensitization when they are injected alone The contact dermatitis form of sensitization is readily induced by exposure of the unbroken skin to the allergen Injection of the allergen deep into the tissues is relatively or completely ineffectual in producing this type of sensitization

Arthus Reaction

The Arthus reaction is the local reaction of an anaphylactically sensitized animal to an intracutaneous or subcutaneous injection of the specific antigen When observed with the unaided eye this seems to be a delayed reaction with no change visible for several hours then there is seen gradual development of edema which progresses to ecchymosis and after twenty four hours or more necrosis of the tissues When observed with a microscope however the reaction is seen to begin within a few minutes after the injection of antigen with slowing of the circulation of small blood vessels formation of thrombi and disintegration of their walls The reaction visible to the unaided eye reflects the gradual escape of plasma and blood through these damaged vessel

Shwartzman Sanarelli Phenomenon

The phenomenon described by Sanarelli (8) as hemorrhagic allergy and studied in detail by Shwartzman (9) pathologically resembles the Arthus reaction but actually is not an allergic or an antigen antibody reaction To produce this reaction a bacterial filtrate is injected into the skin of a rabbit and twenty four hours later the same or another filtrate is injected intravenously The characteristic reaction is a hemorrhagic and necrotic lesion at the site of the initial intracutaneous injection From the time interval used it is apparent that no antibody can be developed from the fact that the intracutaneous and intravenous injections need not be of the same material it is apparent that the reaction is not specific in the immunologic sense

Serum Sickness and Arteritis

Since serum sickness is a manifestation of anaphylactic sensitization it is classed with the immediate type of reaction although the symptoms commonly occur a week or more after the injection of heterologous antiserum This delay represents the incubation period of antibody formation As the antibodies are formed their reaction with the remaining antigen is immediate During this reaction which may continue over several days as antibody is formed and antigen is eliminated scattered lesions of the smaller arteries with degeneration of the media and necrosis may develop

Similar lesions are seen in cases of allergy to sulfonamides and other drugs. The similarity of these lesions to those of *periarteritis nodosa* has lent strong new support to the old hypothesis that periarteritis nodosa is a manifestation of allergy (10). While this theory seems to fit many of the observed facts satisfactorily, the allergic approach has so far contributed little to the therapy of periarteritis nodosa. In no cases of the disease arising spontaneously, without previous use of drugs, has a specific allergen been proven to be the causative factor. The evidence that allergy may be a factor in other collagen diseases—disseminated lupus erythematosis, rheumatoid arthritis, acute rheumatic fever and dermatomyositis—is also strongly suggestive but not conclusive.

Allergy to Infective Agents

The delayed type of allergy to infectious agents, of which the tuberculin reaction is the classic example, has been shown to develop in a wide variety of infections by bacteria, fungi, spirochetes and viruses. Both acute and chronic bacterial infections, including brucellosis, tularemia, typhoid fever, glanders, chancroid and streptococcal, staphylococcal and pneumococcal infections, may lead to this type of sensitization to the organism. All of the systemic fungus infections and, in most cases, even minor fungus infections of the skin are accompanied by sensitization to the organisms. Among the virus diseases the phenomenon is most marked in lymphopathia venereum but also develops in the more acute virus infections such as mumps.

In all of these cases, allergy develops as a result of infection and is manifested by injury or necrosis of cells in contact with the organism. In the chronic infections the pathogenesis of the disease may be profoundly altered by change in the reaction of the host to the parasite. This is illustrated by the caseation of tubercles and by the development of gummata in tertiary syphilis after sensitization has become marked. The sensitized person will react specifically to suitable antigens, generally proteins, from the causative organism by a delayed inflammatory reaction to a skin test. These skin tests are often of diagnostic value, but the sensitization persists indefinitely and is not necessarily evidence of active infection.

There is some evidence that bacteria may also cause immediate types of sensitization, but the information concerning these is less complete. Before the use of sulfonamides and antibiotics it was noted that recovery from pneumococcal pneumonia was accompanied by the development of an urticarial reaction to a skin test with the specific polysaccharide of the type of pneumococcus involved. This reflected the development of specific precipitins and an immediate type of sensitization. Such immedi-

ate skin reactions to other bacterial antigens are not commonly observed, possibly this is due to uncertainty as to the most suitable type of antigen for skin testing

Certain cases of asthma allergic rhinitis and urticaria are definitely influenced by bacterial infections Skin tests with the available bacterial antigens in such cases generally do not show diagnostic reactions of the immediate type Occasionally the intracutaneous test produces a systemic exacerbation of symptoms showing evidence of bacterial allergy—but even in these cases the local reaction to the test may be negative

Another phase of bacterial sensitization that remains unsettled is the relationship of streptococcus infection to rheumatic fever This relationship has been indicated by a variety of clinical pathologic and experimental studies but the nature of the immunologic mechanism has not been established

RELATIONSHIP OF BACTERIAL ALLERGY TO IMMUNITY

Whether or not allergy to bacteria and other infective agents plays a part in immunity to infection has been the subject of considerable difference of opinion While the question is not yet completely settled the preponderance of evidence suggests that bacterial allergy is not an effective factor in immunity All species of bacteria which have been studied in detail have been found to contain several different antigens each of which may evoke specific antibody responses For example the pneumococcus is known to contain the capsular polysaccharide (SSS) which is type specific and also the somatic carbohydrate C antigen nucleoprotein and Forssman antigen all of which are species specific Resistance to infection is apparently determined only by the antibody related to the capsular carbohydrate On the other hand the antigen producing the reaction of delayed bacterial allergy in the case of the pneumococcus is the nucleoprotein Since immunity and allergy are related to entirely different antigens it is apparent that one plays no part in the other In none of the pathogenic organisms adequately studied have delayed bacterial allergy and immunity been found to be related to the same antigen of the organism

AUTOSENSITIZATION

Most of the antigens of the body tissues and fluids are *species specific* This means that they are different for each species and act as antigens in other species of animal but not in the one from which they are derived Certain of the tissues such as the lens of the eye and the brain contain antigens which are *organ specific* rather than species specific Under certain conditions antibodies specific for the tissue or organ antigens may be formed by the organism from which they are derived Experi

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mentally these may be produced by injection of tissue antigens in conjunction with bacterial toxins or adjuvants Similar sensitization to antigens of one's own tissues or *autosensitization*, may occur spontaneously as a result of infections Donath and Landsteiner (11) showed that syphilitic infection occasionally led to the formation of a hemolysin which combined with the individual's own red blood cells at low temperatures to produce paroxysmal hemoglobinuria Autohemagglutinins reacting with one's own cells at low temperatures have also been shown to be formed *in virus pneumonia On the basis of the Coombs antiglobulin reaction* it is believed that many cases of acquired hemolytic anemia are due to autohemolysins

The encephalomyelitis which occasionally follows the injection of rabies vaccine derived from rabbit nervous tissue has been attributed to the development of antibodies reacting with autogenous brain antigen and thus causing tissue damage There is experimental evidence to suggest that the sensitization in rheumatic fever is not to the streptococcus but is an autosensitization induced by the streptococcus infection and that a similar mechanism may also be involved in the pathogenesis of glomerular nephritis Thus the role of autosensitization as the causation of disease appears to be important its actual extent remains to be established

PHYSICAL ALLERGY

In certain patients reactions which have features suggestive of allergic disease—especially urticaria—are precipitated by exposure to physical agents *(heat cold light or mechanical irritation) rather than to a specific* material allergen These reactions have been described as physical allergy Some of these reactions (to cold or light) are apparently truly immunologic phenomena since the serum contains *skin sensitizing antibodies* capable of inducing in normal skin a reaction to the same physical agent The actual antigen is presumably an autoantigen of the tissues either altered in its specificity by the effects of the physical agent or reacting with the antibody only under certain physical conditions As mentioned in the discussion of autosensitization *autoantibodies reacting with red blood cells only* in the cold have long been recognized It seems reasonable to assume that similar antibodies related to other tissue antigens may exist

In other cases allergic reactions to specific extrinsic allergens are precipitated or so augmented by physical influences that the importance of the material antigen may be overlooked This is true in some cases of cold urticaria and probably in most cases of rhinitis or asthma apparently due to physical factors

Still other reactions generally classed as physical allergy seem to be due to an exaggeration of the normal release of histamine in response to

physical stimuli, with little or no evidence of the existence of an immunologic mechanism

ALLERGY TO DRUGS

It has long been recognized that some forms of drug idiosyncrasy were entirely unrelated to the normal pharmacologic actions of the drug and closely resembled allergic reactions. Sensitization was acquired through use and after it developed further exposure to small doses induced a reaction. Other types of abnormal reactions such as hyperreactivity to the typical pharmacologic or toxic effects of the drug bear no relation to allergy or hypersensitivity in the immunologic sense.

Many of the botanical and biological drugs contain protein antigens which may elicit the usual allergic reactions in the same manner as foods or inhalants or induce anaphylactic sensitization when injected parenterally. In sensitive patients these protein drugs usually give positive skin tests which are of diagnostic value.

The nonprotein drugs which are not antigens but presumably act as haptens may also cause contact dermatitis, urticaria, rhinitis, asthma and anaphylaxis, but in addition cause a variety of other manifestations of sensitization which are not known to be produced by other types of allergens. Among the most common of these are drug fever and dermatitis medicamentosa, which may occur separately or together. Often associated with these conditions are necrotizing arteritis and hepatitis. Certain drugs appear to combine as haptens with the leukocytes or platelets of the blood and induce the formation of antibodies which react with these elements to cause leukopenia or thrombocytopenic purpura.

In contact dermatitis due to drugs patch tests with the causative allergen are usually diagnostic. Aside from this one form of sensitization skin tests with nonprotein drugs are rarely helpful and may involve risk of inducing a serious general reaction. In other forms of drug allergy the diagnosis is based primarily on the knowledge of the types of reactions most often observed with each drug.

PHYSIOLOGIC FACTORS AFFECTING ALLERGIC PHENOMENA

Although the fundamental basis of the allergic reaction is the union of antigen and antibody, the physiologic and pathologic manifestations resulting from it may be markedly influenced by changes in the physiologic state of the body—especially of the shock organ.

Among such influences are those of the endocrine glands, particularly the adrenals. Allergy is not caused by [illegible] endocrine glan[illegible] [illegible]rtica[illegible] most allergic patients have normal [illegible] of the [illegible] forms of allergy are [illegible]adily [illegible] an[illegible] However animals fro[illegible]

unusually susceptible to anaphylactic shock and an excess of adrenal hormones over the normal supply tends to inhibit many forms of allergic reaction

The adrenal medullary hormone epinephrine through its marked effects on the blood vessels smooth muscles and glands innervated by the sympathetic nervous system inhibits to a greater or less degree most of the allergic reactions of the immediate type which are manifested largely by physiologic changes in these tissues This action of epinephrine (and such related drugs as ephedrine) plays an important part in the symptomatic relief of allergies of this group *These drugs do not have any significant* effect on the delayed type of allergic reactions which is essentially cellular and in which the blood vessels and smooth muscles are not important

The adrenal cortical hormones cortisone and hydrocortisone have inhibitory effects on a wide variety of allergic reactions of both immediate and delayed types The same effects produced by administration of exogenous cortical hormones are also accomplished by stimulating the secretion of endogenous cortical hormones with the pituitary adrenocorticotrophic hormone ACTH or corticotropin These hormones tend to inhibit the formation of antibodies and thus inhibit the development of experimental anaphylactic sensitization When given to fully sensitized animals their effect on anaphylactic shock and the Arthus reaction is relatively slight in most species studied In clinical use these hormones are of great value in inhibiting to a greater or lesser extent the symptoms of practically all of the atopic diseases In adequate doses they also inhibit the tuberculin reaction and contact dermatitis The remissions of chronic allergic disease which sometimes follow acute illnesses and major operations for unrelated conditions are believed to be due to the increased adrenal cortex secretion which results from stress

Certain forms of allergic reactions such as the anaphylactic reaction and the tuberculin reaction may take place in excised tissues separated from nerve control the nervous system apparently does not play an essential part in allergic phenomena However since the manifestations of the immediate allergic reactions depend largely on the action of blood vessels and smooth muscles whose tone is regulated by the autonomic system the activity of these nerves may augment or inhibit the reactions resulting from allergy of this type Holmes and his co workers (12) *have shown* that blocking the sympathetic nerve supply to one side of the nose in a patient with hay fever greatly increased the reaction on exposure to the specific pollen antigen In general the actions of the parasympathetic nerves parallel the phenomena of the immediate allergic reaction and *those of the sympathetic system are antagonistic*

EMOTIONAL FACTORS

Much has been written about the effects of emotional states on allerg disease Emotional stress in many instances appears to augment allerg symptoms while acute severe stress may occasionally have an inhibitor effect It is believed that these psychic changes act as secondary factor influencing the degree of reaction in latent allergic states basically due to material allergens However the emotional factor is not infrequently the obvious cause precipitating a particular attack and in some cases demonstration of the presumed specific antigen is difficult or impossible In practical management of such patients it is important to recognize the emotional factors but the therapeutic advantage of determining an underlying specific allergen warrants a diligent search for it rather than the easy acceptance of the reaction as a purely psychosomatic phenomenon

There is little evidence available as to the actual mechanism involved in the effect of emotions on allergic symptoms The emotions are known to have important physiologic effects on the autonomic nervous system and on the adrenal glands Since both of these influence the allergic reactions of the immediate type it is possible that the effects of the emotions on allergic phenomena might be mediated by either system

The severity of many allergic reactions is influenced by the degree of physiologic activity of the shock organ For example in bronchial asthma mild latent symptoms may become clinically apparent as a result of increasing the rate and depth of respiration either voluntarily or by physical exercise Symptoms may also be augmented by the effects of nonspecific irritants on the shock organ In asthma basically due to specific allergens attacks may be precipitated by exposure to sudden changes of temperature humidity irritating fumes smoke or nonallergenic dusts Bright light has a similar effect on the conjunctivitis of hay fever

Many attempts have been made to relate allergic symptoms to changes in the composition of the body fluids Attention has been directed to the mineral salts particularly calcium and potassium to the hydrogen ion concentration and to the various vitamins There have been reports of deficiencies in each of these factors associated with allergic disease and therapy directed at correcting these deficiencies has been advised However in each instance more careful studies have failed to show evidence that allergy results from any such deficiency and therapy based on such theories has proved fruitless

SKIN TESTS IN ALLERGIC DISEASE

In chronic allergic diseases satisfactory treatment usually depends upon determining the specific causative agent so that steps may be taken

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2

ALLERGY OF THE CONJUNCTIVA: GENERAL CONSIDERATIONS

There could hardly be a better site in the body than the conjunctiva for the study of basic allergic reactions. The juxtaposition of readily accessible mucous membrane to the adjacent thin and delicate skin of the eyelids provides the opportunity for all types of allergic reactions to occur to an extent and with a frequency that do not exist elsewhere. While the nasal mucosa is often the site of explosive air borne allergies, contact allergy is relatively rare. The reverse is true of the skin. Only in the conjunctiva are both of these forms of allergy, as well as reactions to microbial allergens, commonly encountered. Such allergic responses may result either from local exposure to excitants or as part of a generalized hypersensitivity.

The importance of allergies of the conjunctiva in clinical practice is universally recognized. The frequency of allergic conjunctivitis is explained by the fact that direct contact of allergens with the conjunctiva is a rather common occurrence. The conjunctiva is readily accessible to air borne allergens, is exposed to contactants, is frequently the site of administration of drugs, and is repeatedly infected by various bacteria—of which at least one, the Staphylococcus, is highly antigenic. Yet because allergic conjunctivitis is not a single entity but instead assumes many forms, difficulties in diagnosis arise. Moreover, since certain types of allergic conjunctivitis may resemble conjunctivitis of nonallergic origin, such as bacterial and viral infections, on many occasions the diagnosis of allergic conjunctivitis is either not entertained when allergy occurs or else is made erroneously when no allergy exists. As a result, unnecessary problems in the management of these patients may arise.

The different types of response that allergy may evoke in the conjunctiva cannot be understood and delineated unless basic allergic principles (cl ap 1) are accepted Once the conjunctival manifestations of allergy are correlated and classified in this manner in accordance with the allergic mechanisms involved many seemingly bizarre and apparently inexplicable clinical phenomena become clear thus resolving otherwise troublesome diagnostic and therapeutic difficulties

This chapter will deal first with the basis for the occurrence of allergic reactions in the conjunctiva and then will develop a practical classification of conjunctival allergies utilizing fundamental allergic concepts Detailed discussion of the various types of allergic conjunctivitis will follow in subsequent chapters

THE BASIS FOR THE ALLERGIC REACTION

There have been three separate approaches in the investigation of allergies of the conjunctiva 1) the study of hay fever 2) immunologic studies and 3) clinical investigations Chronologically clinical and experimental observations concerning hay fever preceded by far all other avenues of investigation In fact this disease was placed on a definitive etiologic basis long before the concept of allergy as a pathologic mechanism was established Thus a more or less detailed discussion of the evolution of modern concepts concerning hay fever offers an excellent jumping off point for the consideration of allergic conjunctivitis in general

History of Hay Fever

The earliest observations on conjunctival allergic reactions apparently concerned allergy to pollens In a masterful presentation of the history of hay fever Thommen (1) quotes Ledelius and de Rebecque who both in 1683 and 1691 respectively described ocular reactions to roses with itching and edema of the conjunctiva as well as copious tearing occurring only when roses were in bloom Much later (1819) Bostock in a classical paper entitled Case of Periodical Affection of the Eyes and Chest established hay fever as an entity This author reported more cases in 1828 but attributed the condition to heat and sun rays Although subsequent authors pointed out the connection with greenhouses and grasses and although the popular lay notion that hay fever was probably due to the pollen of flowers and grasses was recorded medically as early as 1831 little was established concerning the causation of hay fever until *Blackley s* classical contributions appeared in 1873 This author like Bostock himself a sufferer from the disease conducted brilliant auto experiments and made astute clinical observations over a period of fourteen years in order to establish that the midsummer variety of hay fever occurring in Great Britain was due to the pollen of grasses

Meanwhile (Swett 1852) it had become apparent that hay fever in the United States occurred mostly in the late summer and the fall. That this particular type of hay fever was due to ragweed pollen was shown in 1872 by Wyman, another hay fever sufferer who reproduced hay fever in himself, his family and others while symptom free in the White Mountains by means of ragweed he had brought with him for this purpose.

Despite all this, which today would appear to be conclusive proof of the cause of hay fever, medical thought of the era was not ready to accept such an explanation; others advanced suggestions that the condition was 1) a neurosis, 2) due to microorganisms (as great an authority as Helmholtz!) and 3) due to a pathologic condition of the nose. These erroneous hypotheses were particularly unfortunate not only because they resulted in almost universal lack of recognition of contributions by brilliant men far ahead of their time but because they channelled therapy in the wrong direction for decades. Blackley's misfortune was that medical thinking was just becoming bacteriologically oriented at the time and that the scientific world's attention was focussed on the exciting revelations as to disease etiology unfolded by the work of the pioneers in microbiology and the resultant rapid strides made in prevention and treatment of disease. Offering neither a new bacterium nor, perhaps more important, a new treatment for hay fever, Blackley's contributions fell on unreceptive ears. A positive approach such as intranasal surgery had a stronger appeal. Ironically, it is interesting that the only ones who gave hay fever the attention it deserved were those who appreciated from personal experience the misery it causes.

So the matter stood for the last thirty years of the nineteenth century. It remained for Dunbar in 1903, followed by others (1), to demonstrate beyond all reasonable doubt that hay fever was caused by pollens. This was achieved by a series of ocular as well as other experimental findings. The interest that Dunbar's work stimulated was heightened by the specific method of treatment that he proposed, incorrect as it turned out to be. Producing a supposedly specific immune serum ("Pollantin") in animals by injection of pollen extracts, he used this serum for passive immunization of hay fever patients. This was followed by "Graminol," obtained from unvaccinated herbivorous animals by Weichardt. Neither was any good, but for more than ten years they were the methods of choice in treatment until their shortcomings were finally recognized.

Modern treatment of hay fever was initiated in 1911 by means of active immunization with subcutaneous injections of pollen extracts by Noon and Freeman. Histamine antagonists were introduced about thirty years later, in the forties; steroids another ten years after that.

This summary points out some interesting object lessons. These include the importance of timing in the acceptance of new ideas, the pitfalls of dogmatism and of misinterpreted observations, and how false premises may so effectively motivate a system of therapy that it undeservedly attains universal and long standing acceptance. Many similarities to our present day problems in regard to vernal conjunctivitis will become apparent.

Immunologic Studies

Although a considerable amount of clinical information in regard to the conjunctivitis accompanying hay fever, as well as that resulting from drug intolerance, as will be noted below, was thus already available before the turn of the century, the explanation of these noninfectious inflammatory reactions of the conjunctiva was not yet at hand. However, once Portier and Richet's (2) experiments with toxins had demonstrated animal anaphylaxis in 1902, and the work of Arthus in 1903 (3) had elicited similar reactions with nontoxic agents such as normal or foreign serum, and von Pirquet's (4) clinical and experimental observations of human beings had laid the groundwork for our understanding of modern allergy, numerous experimental studies in the field of ocular hypersensitivity were soon undertaken. Space will not permit a complete summary of these; only those with a direct fundamental bearing on the subject will be mentioned.

The earliest work was well summarized by von Szily in 1914 (5). Romer, Stanculeanu and Nita, Dold and Rados, and Colombo all used horse serum as the sensitizing antigen for the conjunctiva of dogs or of guinea pigs. In each experiment subsequent subconjunctival injection or simple topical instillation of serum resulted in reactions demonstrating that the conjunctiva has the same absorbent capacity and the same sensitizing tendencies of other mucous membranes and that it can be the site of anaphylactic reactions.

The occurrence of fatal anaphylaxis in horses as a result of conjunctival instillation of ascaris toxin was reported by Weinberg and Julien in 1913 (6). Allergic conjunctival reactions to other helminthic products, as well as ascaris, were demonstrated in infested horses upon conjunctival instillation by van Es and Schalk in 1918 (7). In control animals reactions did not occur.

In 1927 Ratner, Jackson and Gruehl (8) reported that ten per cent of previously sensitized guinea pigs developed an acute immediate form of conjunctival allergy with purulent discharge lasting up to one and one half hours if exposed to an atmosphere containing the same allergenic protein dust or if reinjected with the protein.

That passive local sensitization of the conjunctiva could be accomplished

was demonstrated by Walzer Sherman and Feldman in 1935 (9) Of each of thirteen of their patients, one eye was sensitized to ragweed by subconjunctival injection of serum from a hay fever patient five others were sensitized to rabbit dander with the serum of an asthmatic who was allergic to rabbits In each instance every patient showed reactions when the correct allergen either extract of pollen or rabbit epithelium was instilled in the conjunctival sac two to ten days later The experiment indicated that passive sensitivity could be induced in the conjunctiva could persist for from one to five weeks and could be neutralized by one test or repeated tests with the specific antigen

An interesting passive transfer experiment reported by Chait in 1950 (10) should be mentioned An intradermal injection of serum from an individual who was very sensitive to peanuts was made in a child with complete dacryostenosis Twenty four hours later a pledget of cotton soaked with peanut extract was placed in the child's lower conjunctival sac A reaction appeared at the sensitized area of skin in twenty one minutes This indicated that the conjunctiva may also serve as a portal of entry for allergens causing systemic reactions

According to Sherman and Feldman (11) intramucosal injections of antigens in the conjunctiva result in responses ten times more sensitive than intracutaneous injections and one hundred times more sensitive than by instillation in the conjunctival sac They suggest that such intramucosal tests be performed in clinical allergies where skin tests have been negative Since even conjunctival drop tests often result in most extreme reactions and may be hazardous this method should be used with great caution

In summary these experimental highlights confirm what Woods (12) has so clearly stated that the eye will develop local allergic inflammatory reactions if 1) in the generally sensitized body the antigen is later brought in direct contact with the ocular tissues or 2) if an increased local hypersensitivity has already been produced by primary sensitization of the eye and the antigen later reaches the eye from systemic absorption Unless the conjunctiva has been especially sensitized by direct contact later systemic absorption of the allergen usually produces no conjunctival reaction Thus in most cases allergic conjunctival reactions imply that at one time or another the conjunctiva has been exposed to direct contact—by inoculation or infection—with the allergen

The Evolution of Allergic Conjunctivitis as a Clinical Entity

The earliest clinical reports other than those on conjunctival hypersensitivity due to hay fever noted above were concerned with drug intolerance since the introduction of the concepts of anaphylaxis and allergy

was still more than a generation away the essential nature of the reactions was of course unappreciated That did not prevent some excellent clinical observations in which the occurrence of individual intolerance was brought out although the contamination of solutions by molds was also thought to be important As far back as 1855 von Graefe (13) alluded to atropine reactions from long usage Later in 1864 (14), he devoted several pages to an excellent clinical description of dermatoconjunctivitis from atropine and recorded the recurrence of symptoms months after the conjunctivitis had subsided when the drug was used once again

Reactions to eserine were mentioned in passing in an excellent paper on atropine intolerance by Galezowski in 1875 (15) he observed that eserine seemed more irritating than atropine and very likely to cause conjunctivitis Follicular conjunctivitis from eserine was also observed by Jany in 1878 (16) and by Cohn in 1895 (17) The occurrence of eczema after prolonged usage was recorded by Pfluger in 1882 (16)

A short report by Mittendorf concerning allergic dermatoconjunctiviti from continued use of cocaine was made in 1888 (18) Three cases were described

In 1912 Weill (19) pointed out that atropine eczema was a manifestation of anaphylaxis and found patch tests on the forearm to be positive in some cases Michail (20) however claimed to have been the *first to report (in 1924) a case under the definite title of atropine* anaphylaxis His patient developed corneal lesions and conjunctival eosinophilia as well as severe pseudomembranous dermatoconjunctivitis When hyoscine was substituted a similar allergy of comparable severity also eventually occurred

In general however—although by the second decade of this century allergy was an established and accepted concept and as we have seen conjunctival allergy had been proved experimentally—little or nothing had appeared in the medical literature concerning allergic conjunctivitis as such except in regard to hay fever and drug reactions A possible exception was the report of Thilliez in 1898 (21) who observed two instances of severe edema of the bulbar conjunctiva and lids in a patient with alimentary intoxication This understandably incomplete and—to our minds—inconclusive report would presumably implicate food allergy (white meat poultry milk) as the cause Other ocular reactions resulting *from the ingestion of foods are recorded as occurring even earlier* by Lewin and Guillery (16) but in each instance the food concerned was believed to have been spoiled One must therefore assume that these were instances of food poisoning although some might well have been allergies

The first definite report of conjunctivitis due to food allergy was made by Conlon in 1919 (22) In his cases the conjunctivitis was of a more

chronic less edematous type In one patient the allergens were strawberries and tomatoes including catsup Another patient perhaps the most clear cut instance was sensitive to eggs The third patient reacted only on fishing trips when at every meal he ate the flounders he had caught Allergy to fish was noted by Prausnitz and Kustner in 1921 (23) as a cause of conjunctivitis and allergy to apricots was noted by Strebel (24)

Other case reports soon followed indicating the wide latitude for allergic reactions possible in the conjunctiva Allergy to oak as the cause of severe recurring conjunctivitis and eczema of the eyelids face and hands was described as occurring in a wood cutter by Lagrange in 1922 (25) This author in conjunction with Delthil continued studies on allergic conjunctivitis and vernal catarrh in a series of communications following this (26) they emphasized the importance of terrain and diathesis especially endocrine factors and described cases of acute allergic conjunctivitis resulting from proximity to animals such as dogs cats and horses and also to the wool of sweaters The occurrence of acute conjunctival allergic crises during asthmatic attacks in two patients sensitive to cats in two patients allergic to horses and in one patient allergic to wheat was recorded by Vallery Radot Blamoutier and Stehelin in 1929 (27) This was added evidence that acute edematous conjunctival reactions were the ocular counterparts of the naso bronchial crises of the immediate forms of allergy

That animal blood other than horse serum as well as animal dander could cause allergic conjunctivitis was illustrated by Blake s report in 1924 (28) The patient was a medical student who developed a hyperacute conjunctival reaction immediately after cat blood had spurted into one eye Tests revealed marked skin sensitivity to rabbit cat and horse epidermis and the patient gave a history of roughening and itching of the skin whenever it was licked by a cat or a dog Manger s case (29) was somewhat different It concerned a pharmacologist who always had asthma after bloody operations on cats (but never from handling uninjured ones) Within a few seconds after cat s blood entered his eye a most marked reaction occurred characterized by edema injection pruritus and photophobia Conjunctival reactions to horse serum had been of course well known for some time previous to this

The importance of pollens and foods as major causes of allergic conjunctivitis was stressed by Woods in 1924 in an analysis of his observations in this field (30) In this paper Woods also described a severe kerato conjunctivitis due to allergy to corn following scratching of the cornea by a blade of corn healed only by desensitization by corn pollen

The early thirties saw ever widening recognition of the importance of allergic conjunctivitis even though all forms of allergy of the outer eye

under this heading is essentially clear cut, the allergic causes, effects and mechanisms are unquestioned, uniform and entirely predictable in accordance with a definite antigen antibody response This is very different from the situation that exists in so called atopic dermatitis (neurodermatitis), where a characteristic form of dermatitis occurs in atopic individuals In this disease, as in vernal conjunctivitis where a similar background exists the antigen antibody relationship is by no means a regular or established one, especially after the first two years of life Any reaction occurring in the course of atopic dermatitis, ocular or otherwise is best described as a complication of the disease rather than an atopic reaction except where a known antigen evokes a demonstrable immediate type response—as may, of course, occur in any atopic individual suffering from multiple allergies

We maintain this distinction between true atopic reactions and those occurring in association with atopic dermatitis in our discussions of allergy of the cornea (chap 15) and the so called 'atopic cataract (chap 20)

The other two major categories of allergic conjunctivitis (table 2) are basically manifestations of delayed allergy One type is due to microbial allergy and the other to contact allergy In both forms there is an absence of humoral antibodies the involved cells themselves are the seat of the antigen specific reaction Passive transfer rarely occurs Histamine plays little or no role in the reaction

As the name implies the term microbiallergic conjunctivitis is used to describe those reactions due to microbial (usually bacterial) allergy resulting from products derived from all types of microorganisms bacterial fungal parasitic and possibly viral Such allergy is essentially of the delayed (tuberculin) type occurring at least several hours (usually twenty four to forty eight) after exposure Under certain circumstances immediate reactions may be noted on intradermal tests but these responses are not typical and are generally minor However bacterial toxins mold spores and parasitic products under special circumstances may give immediate type allergic reactions (chap 3)

The term allergic dermatoconjunctivitis is used to describe reactions of the conjunctiva resulting from contact allergy—usually to locally applied drugs or chemicals In this delayed reaction patch tests not *intradermal tests require a matter of hours (often twenty four to forty* eight) to become positive Eczematous dermatitis of the eyelids is a characteristic and diagnostic part of the clinical picture

These three basic forms of allergic conjunctivitis are considered at length in the following chapters

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3

ATOPIC CONJUNCTIVITIS

This type of conjunctival allergy is basically a form of the immediate type of hypersensitivity On almost every occasion the reaction is atopic, actual anaphylaxis is very rare A familial history of allergy (atopy) is generally obtained The patient usually exhibits other manifestations of allergy The conjunctivitis is caused mainly by the air borne group of allergens of which pollens are the most important Other responsible inhalants include animal epidermal substances, certain nonpathogenic fungi mites and dusts Atopic conjunctivitis may also result from the ingestion of foods, or from either contact with or the internal administration of animal proteins or sera The conjunctival reaction is similar to the inflammatory edema which may involve the entire respiratory tract in susceptible individuals such as persons suffering from hay fever and asthma, and occurs in a matter of minutes after exposure to the sensitizing substance Skin tests of the intradermal or scratch types give positive immediate wheal responses in most cases of this group Passive transfer experiments are positive Ophthalmic tests (fig 1) which make use of the direct instillation of the suspected allergen in weak dilution (such as 1 500) must be performed with great caution In highly sensitive individuals, especially when such tests are repeated severe and possibly permanent, ocular damage may result As soon as the reaction has occurred epinephrine (1 1000) *or other vasoconstrictors should be instilled The pathologic physiology* of the process is essentially vasodilatation and increased capillary permeability Histamine plays an important role in the process as it does in all other forms of the immediate types of allergy Eosinophiles occur in abundance in the secretion (which is generally watery, but may become mucopurulent) and in epithelial scrapings of the conjunctiva

From the clinical point of view atopic conjunctivitis may be divided into two varieties 1) an acute explosive variety, often having a highly



Fig 1 Experimentally induced conjunctivitis in ragweed sensitive hay fever patient A small amount of pollen (still visible) was placed in lower conjunctival sac 7 minutes before picture was taken

distinctive and diagnostic appearance (Plate I, figs 1–3) and 2) a chronic low-grade reaction superficially often indistinguishable from other types of chronic conjunctivitis (Plate I, fig 4) Since the allergic mechanisms and the exciting agents are the same and since intermediate subacute varieties are often encountered it is felt that both varieties should be *considered as manifestations of one entity even though they may appear* so different from each other The responsible allergens will be discussed after the clinical characteristics of both forms of atopic conjunctivitis are described

ACUTE ATOPIC CONJUNCTIVITIS

Acute atopic conjunctivitis is characterized by a sudden or immediate hyperemia and edema of the conjunctiva causing intense almost intolerable irritation itching burning and photophobia Except for the rare occasion when the antigen contact is limited to one eye only, the reaction is bilateral The chemosis often gives the eye a glassy appearance and may become extreme covering the entire cornea The inflammatory reaction in the conjunctiva is in our experience almost always of the papillary type unaccompanied by preauricular lymphadenopathy While some observers (1) report follicular reactions in special instances these unusual cases would appear to be of the chronic atopic variety The reaction is

accompanied by profuse tearing the discharge while generally watery often becomes mucopurulent Marked conjunctival eosinophilia is the rule

The combination of the explosive nature of the conjunctivitis with the dramatic circumstances sometimes occasioning the reaction such as the mere approach of an animal has highlighted this form of allergic conjunctival reaction perhaps more than the facts warrant If we exclude the large majority of those cases occurring in hay fever or due to other pollen allergies acute atopic conjunctivitis is a relatively rare occurrence in actual clinical practice The pollen allergies generally should be considered as instances of chronic (or possibly sub acute) atopic conjunctivitis—unless the tempo is altered by extraneous circumstances Similarly allergic reactions to feathers are generally of a less acute character than those due to other animal epidermals Conjunctival reactions of an acute nature following the local instillation of a foreign serum especially horse serum are well known they have long been used as a test before the administration of antitoxins as well as a test for other allergies

Diagnosis

One of the problems in differential diagnosis is early epidemic keratoconjunctivitis (fig 2) Since chemosis often is the most outstanding finding at the onset of this highly infectious condition it is most important to distinguish it from acute atopic conjunctivitis The virus infection almost always is associated with obvious preauricular lymphadenopathy Mono



Fig 2 Epidemic keratoconjunctivitis The early edematous appearance of this virus infection is easily confused with an acute atopic conjunctivitis

nuclear leukocytes, instead of eosinophiles, are found in the epithelial scrapings. The local use of vasoconstrictors or the systemic administration of antihistaminics are usually very effective in acute atopic conjunctivitis both objectively as well as subjectively, whereas in viral infections they are ineffectual.

Sometimes tenonitis may have to be differentiated, but this is a rarely encountered entity. Ocular trichiniasis should be easily differentiated because it is accompanied by pain on moving the eyes and by local tenderness.

It is our feeling that the acute inflammatory reaction of the conjunctiva occurring following the entrance of eel blood (2) into the conjunctival sac is a direct toxic or irritative one, not a fish allergy. No special idiosyncrasy appears necessary; it seems to occur routinely whenever a person is exposed. The irritant or toxic substance in the eel blood is destroyed by heat (3). Acute conjunctival reactions from other strong irritants such as lime, lye, ipecac, etc., may at times simulate acute atopic conjunctivitis, more so because massive conjunctival eosinophilia may likewise be present. However, the localization of the reaction to the exposed area, usually the lower lid, as against the diffuse response of allergy, which involves the entire conjunctiva of both the upper as well as the lower lids, in addition to other findings and the history, generally make the diagnosis easier (4).

Management

The management of acute atopic conjunctivitis will be considered later (chap. 7) under the treatment of allergic conjunctivitis in general. It may be pointed out here that 1) because it is an exudative response with vasodilation, vasoconstrictors used both locally and systemically give the most rapid immediate relief of all medicaments (figs. 3 and 4); 2) because histamine plays a role in the pathologic physiology, antihistaminics are useful when given systemically, not locally; and 3) because it is a manifestation of the immediate form of allergic response, desensitization is often successful where the fundamental basic treatment of all allergies, elimination of the cause, cannot be accomplished. Blocking agents like the steroids are valuable, but not so dramatically as are the vasoconstrictors.

CHRONIC ATOPIC CONJUNCTIVITIS

In contradistinction to the often dramatic and generally severe reactions that occur in acute atopic conjunctivitis, the chronic form frequently shows little or no objective evidence of inflammation in comparison to the irritating subjective symptoms of itching, burning, photophobia and dryness that are usually present. As a result the patients often are considered psychoneurotic or else are thought to be suffering from chronic catarrhal



Fig 3 (*above*) Ragweed reaction (same patient as in fig 1 after 22 minutes) Less reaction in left eye because of intensive pretreatment with topical cortisone

Fig 4 (*below*) Ragweed reaction (same patient as in figs 2 & 3 after 65 minutes) Epinephrine was instilled 5 minutes before taking this picture and gave immediate relief

conjunctivitis Actually since many cases of chronic conjunctivitis are found bacteriologically negative it may be that a significant number of such so called cases actually are overlooked forms of chronic atopic conjunctivitis In fact even when the ophthalmologist is alerted to the frequency of chronic atopic conjunctivitis if he performs routine epithelial



Fig 5 Chronic atopic conjunctivitis cause not determined Severe itching slight chemosis conjunctival eosinophilia

scrapings in conjunctivitis he is often surprised to find numerous eosinophiles in cases that clinically did not appear allergic

The conjunctiva often appears rather pale A minor degree of conjunctival edema may be suggested by the somewhat juicy appearance of the conjunctiva especially in the lower fornix in its temporal portion While the response is essentially papillary follicles may appear in long standing cases—especially where there is relatively little inflammatory reaction In other patients where a more subacute process occurs there may be considerable injection as well as slight chemosis Corresponding to the grade of the reaction in general there may be a slight watery discharge or a mucopurulent one In either event eosinophiles are found on epithelial scrapings always in diagnostic numbers although less numerous than in acute atopic conjunctivitis Chronic atopic conjunctivitis is often known as simple allergic conjunctivitis

Two studies of a condition that seems to be chronic atopic conjunctivitis (although not so named by the authors) must be mentioned principally because of the pathologic investigations that were done

Beigelman (5) has described what he calls chronic edematous allergic conjunctivitis The major conjunctival change is marked edema of the lower transitional folds and the lower bulbar conjunctiva which may later become relatively hard pale and glassy The changes persist throughout the year although the symptoms of itching and lacrimation may become aggravated in warm weather The secretion although scanty con

tains many eosinophiles. Beigelman performed a pathologic investigation in 6 cases and finds mainly capillary engorgement, edema and infiltration with small lymphocytes, plasma cells and eosinophiles. He cites the resemblance to nasal allergic changes which were also found in his patients. We often encounter similar boggy conjunctival changes, not so edematous, in sufferers from chronic inhalant allergies—usually individuals suffering from hay fever or asthma. The condition appears to us to be the conjunctival prototype of a nonspecific vasomotor rhinitis so frequently noted in hay fever sufferers after the season of pollination ends as well as in many other types of patients.

Bourquin (6) has described a recurrent bilateral simple allergic conjunctivitis occurring in Geneva, Switzerland, during the warm season. Often only a slight hyperemia of the transparent conjunctiva is present with fine papillae visible only with the slit lamp. A small preauricular lymphadenopathy is the rule. The absence of bacteria and the presence of conjunctival eosinophilia along with slight blood eosinophilia marked the condition as allergic in his opinion. Histologic examination reveals epithelial and sub-epithelial edema with greatly dilated capillaries and a cellular infiltration in which eosinophiles predominate both in the tissues and in the blood vessels. Plasma cells and polymorphs are present as are basophiles. Although the condition resembles early vernal conjunctivitis and indeed occurs at the same time of the year, no matter how long it persists it never leads to fibrous interstitial changes like vernal conjunctivitis does. Bourquin's cases would seem to us to be due to pollens since most of his patients handled flowers.

Diagnosis

The diagnosis of chronic atopic conjunctivitis is often difficult because the condition may resemble other forms of chronic conjunctivitis, in particular microbiallergic conjunctivitis due to the staphylococcus. The differentiation of these two forms of chronic allergic conjunctivitis is shown in table 3 in chapter 4. The conjunctivitis that occurs often does not permit any ready means of distinguishing between the two types, although there generally are slight differences. However, more important than the appearance of the conjunctiva itself are the history, the finding of the eosinophiles, and the response to certain avenues of therapy, such as local vasoconstrictors, steroids and oral antihistaminics, and if possible the elimination of the cause of the allergy. These clues afford the framework for differentiating chronic atopic conjunctivitis from other forms of chronic inflammation of the conjunctiva.

Braley (7) points out the importance of differentiating local irritation from local allergy in air borne conjunctivitis. He believes that local irri

tation due to lime dusting powders tree sprays and other substances may be confused with true allergy Since these *local irritants produce conjunctival edema* and stringy secretion with eosinophilia the differential diagnosis is not always easy He has found that local irritation has the following characteristics 1) hyperemic conjunctiva 2) smooth surface or only slight papillary hypertrophy, 3) severe itching and 4) seasonal occurrence This interesting observation is in agreement with our thoughts on chronic irritative conjunctivitis as described in the discussion of drug irritations of the conjunctiva in chapter 6 Eosinophilia does of course occur in severe chemical irritation of the conjunctiva but we have not encountered it so frequently in milder irritations We would also like to note that irritation by its very nature is less diffuse in its reaction than allergy so that certain irritants may be differentiated by their focal reactivity at the exact area of contact whereas allergies react throughout the entire conjunctiva In regions where smog is a not uncommon occurrence the existence of this entity of local air borne irritative conjunctivitis must be considered

IMPORTANT ALLERGENS CAUSING ATOPIC CONJUNCTIVITIS

Atopic conjunctivitis occurs almost exclusively in individuals allergic to various inhalants or ingestants Some of the more important and instructive aspects of reactions to specific allergens will be considered at this point While conjunctival allergy may not have been recorded as the sole or primary clinical reaction to every one of these sensitizers there is no question that the conjunctiva participates in the general mucosal allergy elicited by all of them In pollen allergy for example any fine particulate matter able to cause respiratory hypersensitivity is of course likely to produce conjunctivitis Similarly most allergens causing extrinsic or atopic asthma can evoke a certain amount of conjunctival response during the attack

Pollens

Of the innumerable plants that pollinate relatively few play a major role in pollinosis or hay fever In the United States tree pollens are the cause of spring hay fever which usually lasts from March to May Grass pollens cause summer hay fever from May to July Five species of grasses are in the main responsible timothy June or Kentucky blue grass orchard top red top and in the southern states Bermuda grass With the exception of the United States grass pollinosis is the most important type of hay fever occurring throughout the world The importance of hay fever from trees and grasses however is far overshadowed in this country by *that due to weeds—that is the autumnal type* which occur from the

middle of August through most of September Weeds unfortunately produce more pollen affect more persons cause more severe symptoms and have a longer season than do trees or grasses In the eastern part of the United States ragweed is easily the major offender in the west the most important weed pollens are those of the sages Russian thistle burning brush western water hemp and the amaranths (8)

Hay Fever

The importance of the various types of seasonal hay fever as the cause of many instances of chronic or subacute allergic conjunctivitis is well recognized This group of allergies is now conservatively estimated to affect between three and five per cent of the population of the United States and is believed to be increasing Most of the time especially in cases of long standing the conjunctival symptoms are limited to moderate itching and some injection of the palpebral conjunctiva Often however in children or young adults the major presenting complaints in early hay fever are ocular (fig 6) and may be severe The nasal symptoms are essentially minimal in these patients and since acute conjunctival symptoms of any type are accompanied by increased nasal discharge the nasal symptoms are frequently overlooked Thus only a careful investigation of the history and the finding of eosinophiles in epithelial scrapings will suggest the possibility of hay fever Curiously enough as the hay



Fig 6 Conjunctivitis due to ragweed hay fever In this patient there were no nasal symptoms

fever returns each year the tempo of the conjunctivitis tends to diminish more than do the nasal symptoms so that many older patients utterly miserable from the generally unappreciated insidious cumulative effects of hay fever are entirely free from ocular symptoms

The conjunctiva Hay fever conjunctivitis generally begins with itching *which starts at the inner canthus* and progresses rapidly over the entire conjunctiva Burning is also experienced and the eyes often feel as if hot sand or dust were in them There is an almost irresistible impulse to rub them but rubbing intensifies the irritation—as does exposure to mild irritants which at all other seasons are entirely innocuous to the patient such as cigarette smoke gasoline fumes paints and various household sprays and cleaners Photophobia may be extreme

Objectively the conjunctival reaction is one of papillary hyperplasia *often limited to the palpebral portion but generally causing suffusion of* the bulbar conjunctiva In some cases chemosis occurs in others a diffusely thickened red fleshy inflammation is present Where the process is severe enough a pseudomembrane is seen This is a velvety inflammation most marked in the lower lid conjunctiva quite different from the cobblestone involvement of the upper conjunctiva and the limbic corneal hypertrophy of vernal conjunctivitis However early atypical vernal conjunctivitis may on occasion resemble hay fever conjunctivitis

Other ocular involvement Corneal *complications are* rare and generally mild Fine punctate epithelial stippling of the cornea may be seen on biomicroscopy According to Strebel (9) minute scales may be noted on the epithelium resembling ruptured epithelial vesicles *Mauksel (10)* however reported a recurrent superficial but severe bilateral keratitis resembling eczematous pannus due to grasses We have encountered at least one instance of recurrent episcleritis in a patient with severe ragweed hay fever which appeared to be related to her allergy We have also observed an ophthalmologist suffering from recurrent bilateral iritis which recurred during the period of his grass hay fever With considerable justification he attributed the iritis to the pollen allergy Ruedemann (11) reported a similar observation his patient who suffered from ragweed hay fever developed a plastic iritis of a mild type with marked photophobia and blurring of vision each year during the ragweed season *This iritic reaction interestingly enough resembles that occurring* in serum sickness as described in chapter 19 Peshkin (12) has treated a patient strongly sensitive to trees and grasses who likewise exhibited seasonal recurrences of iritis over a period of approximately *ten years* After a four year period of desensitization the iritis did not recur

Ruedemann (13) mentioned neuroretinitis with minor recurrence ascribed to hay fever symptoms Other ocular complaints including *pain in*

the eyeball, constriction above the eyes, and frontal headaches are probably all referred from the sinuses or else are neuralgic secondary to such sinus involvement. Sherman (14) has observed retinal edema during the course of severe ragweed hay fever which subsided at the end of the pollen season and failed to recur in subsequent years when the hay fever was treated with pollen injections.

Diagnosis The time of occurrence of the various types of pollen allergy causing hay fever depends on the season of pollination and gives the physician important diagnostic information. However, regional variations affect the onset and length of this season. While the severity of the symptoms is usually well correlated with the pollen count, this index must not be accepted as the sole guide in this respect. Often enough patients experience their worst days when the pollen count is low. This might be explained by short periods of temporarily high concentrations capable of causing a reaction severe enough so that the patient remains sick all day. The highest pollen count often occurs between 9 a.m. and 1 p.m., the period during which most patients have their worst symptoms. Such temporary elevation would not be indicated in the total twenty-four hour pollen count for the day if during the rest of the day little pollen were present. Other influences include wind and weather conditions and the often unappreciated effect of nonspecific factors such as dusts, exhaust gases, smoke, and smoking. Thermal changes also trigger the allergic reaction. In addition, the simultaneous occurrence of other allergies (for instance, food allergies) may aggravate hay fever.

The pollens causing hay fever are almost always windborne. Only in rare instances are insect-pollinated plants responsible. Although some authorities maintain that only group specificity exists, Feinberg (16) believes that in addition to the existence of a common antigen within a group, species-specific antigens may also exist. Such common antigenic relationships correspond largely with botanical relationships. The pollen fraction believed to cause the allergy appears to be protein in nature, although other theories have been advanced.

In addition to giving positive skin reactions to the specific pollens causing the disease, hay fever sufferers often are sensitive both to other pollens which clinically appear unimportant in their particular cases and to substances other than pollen. It is widely recognized that these other sensitivities may be enough to aggravate the hay fever during the pollinating season.

Feinberg (17) states that fifty per cent of ragweed-sensitive patients give a positive reaction to pyrethrum on scratch test, making this closely related plant product (used as an insecticide) the most commonly associated allergen. Foods, according to him, are likewise important, especially

vegetables cereals fruits nuts and condiments (in that order) In the middle western and middle southern sections of the United States pollen sensitive patients are also skin sensitive to fungi This author also mentions epidermal allergens (animal hair wool and feathers) and certain miscellaneous substances including orris root tobacco silk cottonseed kapok flax and acacia as causing reactions in patients with hay fever

Treatment While the general treatment of hay fever especially desensitization lies within the province of the allergist a few words concerning the management of its ocular aspects might be permissible at this point In mild cases the use of combinations of vasocontrictors anesthetics and cleansing agents is sufficient (of course one must avoid the prescribing of allergenic drugs) Thus mixtures containing one drug from each of the following groups are useful 1) epinephrine (1 5000) privine (1 5000) or neosynephrine (1 500) 2) cocaine one third per cent and 3) sodium propionate five per cent or zinc sulfate one fourth per cent At other times hydrocortisone five tenths per cent is preferable Antihistaminics taken systemically not topically may be very valuable If necessary steroids especially the newer ones with fewer metabolic side effects such as prednisone and prednisolone are used Air conditioning is helpful especially during sleep However the best treatment which in this age of fast and cheaper transportation is becoming increasingly available to almost everyone would appear to be a sojourn in a relatively pollen poor area during the height of the hay fever season

Other Plants and Plant Products

Important plant allergens other than pollens include cottonseed kapok powdered orris root pyrethrum and jute It is believed that tobacco allergy which is very rare, is mainly due to the smoke The common conjunctivitis from tobacco smoke in our opinion is an irritant reaction rather than an allergic one Allergies to cereal flours such as rye wheat oat corn etc are common causes of asthma Long standing conjunctivitis due to allergy to rye and white flour was reported in a baker by Bab (18) Acute atopic conjunctivitis from wheat was reported by Vallery Radot and his associates (19)

Dust

Various types of dust (fig 7) may play a role in the causation of atopic conjunctivitis *Occupational dusts* cause reactions in millers threshers bakers carpenters and other wood workers in brush rope harness and mattress makers in pharmaceutical workers and chemists and in workers in many other occupations

Street dust is composed of both inorganic and organic constituents The

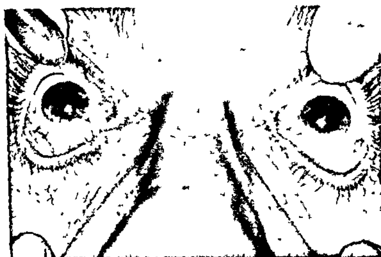


FIG 7 Chronic atopic conjunctivitis due to dust sensitivity

former rarely cause allergies but they may. The organic portion varies with the season and may contain pollens, molds, animal hair, feathers, insects and other constituents.

House dust is a particularly complex material. It contains substances from numerous animal and vegetable sources: feathers, horse hair, rabbit hair, dander from household pets, human dander, all the constituents of clothing, bedding, upholstery and rugs, as well as pollen, plants, bacteria, molds, fungi and insects. Over and above this, it is possible that extract of house dust contains a specific antigenic principle which is not identical with any of its ingredients. Thus allergy may occur from the dust itself as well as from one or more of its components.

Animal Epidermal Substances

These include animal and human dander, hair, hides, sheep's wool and feathers. Allergy to such substances is usually easily diagnosed and relieved. Often the allergy is strictly specific. Indeed, Lagrange (20) reported a case of acute atopic conjunctivitis in a child sensitive to a Siamese cat but not to other cats. A patient allergic to goose feathers may not be affected by a pillow containing chicken feathers. However, group allergy—such as hypersensitivity to all types of feathers or to the hair of every member of the cat family, including wild animals—also occurs. Persons with extreme hypersensitivity may react even when not directly exposed to the offending animal. Asthma has been reported in a patient who suffered an attack every time his mother came home from a horseback ride. Simi

larly, mere traces of horse dander in the air from a near by stable may cause a reaction Horse dander and horse serum contain the same antigen but there is relatively less of it in the dander than in the serum In addition the dander contains another antigen not present in the serum Thus a patient may be allergic to horse dander but not to a horse serum but most people are sensitive to both allergens Acute atopic conjunctivitis from horses was among the first forms of ocular allergies to be reported clinically

Apparently more persons develop conjunctival allergy to cats than to dogs Moreover while allergy to dogs almost always requires the presence of a living animal hypersensitivity to cats can be elicited by any article made from cat fur Cat hair often is found on toy animals

The many usages of rabbit hair give allergy to its dander a special significance In addition, rabbit fur is used extensively as imitations of many more expensive furs Thus exposure to rabbit epidermals is more common than one might think No case of atopic conjunctivitis due to rabbits apart from that occurring in asthmatics has come to our attention

Although allergies to the hair of cows goats camels and hogs and to the hair and dander of guinea pigs mice rats, and monkeys have been known to cause allergic reactions with asthma no instances of atopic conjunctivitis from these have been reported

Sheep s wool usually causes asthma only among those engaged in the wool industry However Lagrange and Delthil (21) have reported a case of atopic conjunctivitis caused by a pullover sweater

The importance of feathers as a common cause of inhalant allergy is reflected in the observations of those (22 23) who have encountered atopic conjunctivitis generally of a sub acute or chronic variety, caused by feathers It is thought that in those instances where the hypersensitivity is limited to the contents of the patient s own pillow the allergy is not due to the feathers themselves but rather to molds mites or even bacterial contamination in the feathers Allergy to feathers may include those of living birds such as canaries and parrots

Urbach and Gottlieb (24) mention allergy to human dander as an occasional cause of hypersensitivity In one instance rhinorrhea occurred whenever the patient a barber combed the hair on a scalp affected with dandruff In another case whenever the patient slept with his wife he developed asthma from her dandruff When this was cleared up the asthma disappeared

Other Inhalants

Insects Inhalant allergy from insects is comparatively rare, it seems to be caused only by those whose wings are covered by scales or hairs of

a type that is easily rubbed off, forming a fine dust that is readily wind borne

Mites Atopic conjunctivitis caused by mites has been reported by Berneaud (23) Asthmatic attacks do not appear to be infrequent Mites are found in grain straw seeds, dried fruits, old upholstery old books and parchment

Silks Inhalation of the silk fiber itself the gum or glue sericin present in raw silk or the silkworm can result in an immediate form of allergic reaction with asthma rhinorrhea and conjunctival symptoms Taub (25) has reported a case of chronic atopic conjunctivitis in the owner of a dress shop who was proved to be allergic to silk Desensitization was successful in her case The allergy was one of inhalation not contact

Parasites The inhalation of protein or other products of parasites may give rise to an immediate form of allergic reaction Urbach and Gottlieb report acquired asthma rhinopathy and conjunctivitis after prolonged exposure to intestinal worms

Fungi The importance of fungi especially mold spores smuts and rusts as a cause of allergy is now well established However wide spread as they are the occurrence of clinical allergy due to them seems to require marked exposure A damp house cellar or ship provides the environment for the high concentration that is needed According to Feinberg (26) who has made important contributions in this field most fungus sensitive patients give a history of aggravated symptoms in the summer months but may also suffer during the winter Symptoms do not coincide with the pollen seasons and are always worse in the country History will reveal an intolerance to yeast containing foods such as beer When molds act as inhalant allergens they evoke an immediate type of allergic response in the same way that pollens do when they act as infective agents they are generally of a pathogenic variety and any allergy that arises is of the delayed bacterial (microbial) type (27) Passive transfer tests are positive in the first type of allergy

Allergic conjunctivitis is common in mold allergy In the diagnosis of such allergy the conjunctival test is widely used causing injection edema and itching when positive Allergic conjunctivitis due to fungi has been reported by Berneaud (23) Simon (28) and Bothman (22) All these authors stressed dampness as a necessary factor Simon's patient was sensitive to Alternaria and Cladosporium giving strongly positive immediate type responses to skin and conjunctival tests Desensitization was effective

Scents There is some evidence that odors can cause inhalant allergies These scents may be of plant animal or synthetic origin Those of plant origin include flowers floral scents used in perfumes fruits and resins Odors of foods may also cause asthma as well as a sort of hay fever Sug-

gestive cases resulting from the smell of vegetable foods such as garlic cabbage apples peas and coffee have been observed (29)

Animal odors usually but not always cause reactions in asthmatics It has been suggested that such allergens are different from epidermal since some patients who are allergic to horse odors are not sensitive to horse dander or to horse hair It is possible that the odors are produced by volatile substances emanating from the sweat and apocrine glands of the skin Like those persons sensitive to the odors of plant foods allergic individuals have developed symptoms from the smell of specific animal foods Urbach and Gottlieb (30) describe extensive angioneurotic edema usually followed by anaphylactic collapse recurring whenever the patient passed a street where a fish market was located These authors quote Kaemmerer as reporting the occurrence of allergic conjunctivitis from the mere smell of fish

We have encountered recurrent allergy characterized by acute atopic conjuntivitis and rhinorrhea brought about by exposure to a very faint scent of heavy perfumes containing musk, the reaction occurred even if the person wearing it had left the room Another patient is so sensitive to wintergreen that the slightest suggestion of it in the air causes similar attacks

Foods

Allergy to foods may cause almost all types of atopic reactions including atopic conjunctivitis According to Rowe (31, 32) one per cent of all food allergies results in ocular reactions Usually the conjunctiva plays only a minor role in the dramatic general systemic reaction that may occur However, conjunctival allergy from foods may not only be quite severe at times but may be the only clinical manifestation of the allergy Both acute and chronic varieties occur Reference has already been made to various case reports of allergic conjunctivitis due to foods (chap 2) Including those cases the following foods have been noted as causing conjunctival allergy eggs milk fish sea foods (fig 8), wheat chocolate (fig 9) rice cereals tomatoes strawberries apricots and other fruits Suggestively allergic reactions from Scotch whiskey (barley) have been noted by us Since practically every food may produce allergy on occasion this list is only a partial one

Several interesting cases of conjunctival allergy due to foods which were not ingested have been reported In Lundberg s (33) case crayfish shell entered the conjunctival sac of one eye of a dish washer who had previously developed hives from eating crayfish or lobster This direct contact resulted in an immediate severe reaction which lasted sixteen hours Berneaud (23) reported a similar instance of acute atopic con



Fig 8 Acute pseudomembranous conjunctivitis due to shellfish Membrane revealed massive eosinophilia

junctivitis from direct contact this occurred in a zoo worker who was allergic only to the variety of fish he fed to his sea lions and not allergic to any other type A particle spurted into one eye

The mechanism of food allergy although it is of the atopic immediate form is more obscure than that of other atopies The reaction time be



Fig 9 Atopic reaction to chocolate

tween allergen contact and the onset of symptoms is considerably longer than in inhalant types and may vary from minutes to hours. In cases of prolonged reaction time it is thought that the person is sensitive to a product of digestion or possibly a newly metabolized allergen. Symptoms may be acute or chronic. Skin tests are often unreliable. Individuals may be allergic to raw foods but may safely eat the same foods when cooked. The reverse also occurs. Food allergy may be either constant or cyclic—that is, it may depend on other circumstances, such as exposure to other allergens (especially pollens) at the same time. Subclinical food allergies may trigger other allergic responses (especially physical) so that they become clinically apparent. Eventual loss of clinical sensitivity to foods permitting their being tolerated once again, is not uncommon.

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4

MICROBIALLERGIC CONJUNCTIVITIS

It is now an established fact that many of the harmful effects that micro organisms can exert in the human body are manifestations of allergy Over and above the direct toxic nature of microbial infection as Rich (1) has put it allergy converts a bacteria that does not produce a toxin into one that does i e, it converts a harmless protein product of bacterial disintegration into a violent and lethal poison " In ophthalmology, such bacterial allergy especially to staphylococcal products is of great importance in diseases of the eyelids conjunctiva cornea and sclera hypersensitivity to products of the Streptococcus and the tubercle bacillus play an important role in uveal diseases and in scleritis

A distinction must be made between microbial allergy and immunity When toxins are absorbed in the course of infection immunity occurs if the body overcomes the invading organisms Such immunity is expressed by the formation of antitoxins Similarly microbial products evoke the formation of different types of immune antibodies such as agglutinins and precipitins In a perhaps oversimplified sense the immunity thus achieved is a protective process, while allergy is an inflammatory and necrotic process which is essentially harmful According to some (2), the difference between the allergic and the immune state is quantitative rather than qualitative depending on the balance between circulating and fixed antibodies and the absence of circulating antibodies The immune state is associated with the presence of circulating antibodies in a concentration sufficient to protect the fixed antibodies also present Another view is that allergy and immunity are independent and unrelated processes that may occur either together or separately

CHARACTERISTICS OF MICROBIAL HYPERSENSITIVITY

While true anaphylaxis identical to that caused by serum has been produced experimentally in animals from large amounts of dead typhoid and

tubercle bacilli, as well as from yeasts, bacterial anaphylaxis as such does not appear to occur in human beings According to the dosage and route of administration hypersensitivity in man manifests itself in local focal or systemic reactions Skin reactions from intradermal injections of microbial products generally are of two types 1) most of the time a delayed allergic response (tuberculin-type) and 2) relatively rarely, the immediate wheal-type response According to Urbach and Gottlieb (3) the latter is seen relatively more commonly in reactions to molds and Monilia than in reactions to bacteria or trichophytin We have found however, that staphylococcal products often cause immediate reactions of this type in particularly hypersensitive individuals A third form of reaction eczematous or epidermal contact type in character may also occur in microbial dermatitis (see chap 13) along with the other two reactions As noted previously passive transfer tests are negative Histamine does not appear to play an important role in the reaction Humoral antibodies are not demonstrable in the sera of patients, instead, antibodies seem to be bound to the cells

While most observations understandably have been made with bacterial and fungal products, enough studies on parasitic agents (helminths) have been done to demonstrate that what might be called infestation allergy to either the tissue protein or excretory products of the parasites occurs as well Clinical cases of allergic conjunctivitis due to helminths will be described later in this chapter Evidence would indicate that such hel-

Diagnosis

skin re-

actions occur in revaccination for smallpox and are useful in mumps Disciform keratitis is believed to be at least in part, an allergic reaction to the virus of herpes simplex according to some investigators

Hypersensitivity to bacterial toxins plays an important part in allergic conditions Burky s (4) staphylococcal experiments, confirmed by others indicate that such toxins may be sensitizing factors even in the absence of allergy to the bacterial protein itself This work is largely the basis for our considering microbiallergic conjunctivitis as an entity

MICROBIALLERGIC CONJUNCTIVITIS DUE TO BACTERIA

There is very little evidence that bacteria other than the Staphylococcus play an important role in the production of allergic conjunctivitis Apparently a combination of two factors operates in the pathogenesis of this condition 1) chronicity with the opportunity for repeated reinfection and 2) the formation of antigenic exotoxin or other sensitizing substances Most bacteria that produce potent but not necessarily allergic exotoxins, such as the diphtheria and tetanus bacilli, cause acute

4

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While most observations understandably have been made with bacterial and fungal products, enough studies on parasitic agents (helminths) have been done to demonstrate that what might be called infestation allergy to either the tissue protein or excretory products of the parasites occurs as well. Clinical cases of allergic conjunctivitis due to helminths will be described later in this chapter. Evidence would indicate that such helminthic reactions are, at least in part, of the immediate variety.

Relatively little has been proved in the field of viral allergy. Diagnosis of lymphogranuloma venereum is aided by a skin test (Frei), skin reactions occur in revaccination for smallpox and are useful in mumps. Disciform keratitis is believed to be, at least in part, an allergic reaction to the virus of herpes simplex according to some investigators.

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processes Only the Staphylococcus appears to fill both requirements in this respect Allergic staphylococcal conjunctivitis will be discussed in detail later in this chapter However it must be emphasized that microbiallergic conjunctivitis may occur without the presence of or previous exposure to what we consider pathogenic organisms Even nonpathogenic bacteria can bring about an allergic state in certain individuals and this fact would explain the occurrence of microbiallergic conjunctivitis where only so called non toxin producing *Staphylococcus albus* is found

The streptococci many varieties of which elaborate both an erythrogenic toxin and hemolysins as well as various antigenic substances derived from the bacteria themselves—such as M and T antigens and also P substances—should also be capable of causing allergic conjunctival reactions Yet *clinical experience does not indicate the necessary repeated exposure* and chronicity noted above We have not encountered any instances in which allergy to products of streptococci has resulted in conjunctivitis—although infectious eczematoid dermatitis of the eyelids due to streptococci does occur on rare occasions (5) and many instances of endogenous uveitis appears to be due to such streptococcal allergy Potvin and Bossu (6) however in their monograph stated that allergic infectious blepharo conjunctivitis may occur from allergy to staphylococcal streptococcal and gonococcal products exotoxins as well as endotoxins but they admitted that difficulties exist in diagnosing allergic streptococcal conjunctivitis Duke Elder (7) also referred to allergic streptococcal conjunctivitis Such entities if they indeed exist are admittedly rare

Although we have not had the opportunity to study such cases it has occurred to us that some instances of so called endogenous gonococcal conjunctivitis of a bygone era may have been allergic rather than metastatic in nature This is supported by our present concepts of uveitis and the characteristics of gonococcal iritis The allergenic substance is presumably gonococcal endotoxin Other chemical components of the gonococcus do not appear to be especially antigenic possibly because the infection stimulates little antibody formation due to its local character However the instillation of gonococcal extracts in the conjunctival sac may produce phlyctenules (8) It is possible that other forms of endogenous conjunctivitis such as have been stated to occur in bacillary dysentery as well as in Reiter s disease are also due to endogenous microbial allergy

The well known Calmette test occurring when tuberculin is instilled in the conjunctival sac of tuberculin positive individuals or animal may be noted as another form of conjunctival allergy to microbial products However in a broad sense clinical allergic conjunctivitis on such basis does not occur except in phlyctenular keratoconjunctivitis which is discussed in chapter 16

As far as is known the other bacteria that frequently cause conjunctivitis, such as the pneumococcus, *Moraxella lacunata* (diplobacillus of Morax-Axenfeld), *Hemophilus influenzae* and the Koch-Weeks bacillus do not cause allergic reaction. It may eventually be found that the allergenic properties of brucella products are responsible for allergic reactions of the conjunctiva. The pneumococcus has been shown to cause other ocular allergic reactions (9).

MICROBIALLERGIC CONJUNCTIVITIS DUE TO THE STAPHYLOCOCCUS

The contributions of Woods (10) and of Burky (4) have established that hypersensitivity to Staphylococcus toxin is the cause of many cases of chronic recurrent conjunctivitis. Clinically these cases, as described by Woods, are characterized by dryness, absence of purulent discharge (Plate I, fig. 5), folliculosis, marginal blepharitis, reddened swollen margins of the eyelids, frequently slight secondary corneal changes, the isolation of a toxin-producing Staphylococcus from the conjunctiva, and the presence of a high degree of cutaneous sensitivity to Staphylococcus toxin. Positive cultures need not occur; sometimes, even when all the other criteria for diagnosis are present, such cultures show no staphylococci on repeated tests—in these cases the staphylococci have been eradi-



Fig. 10. Microbiallergic conjunctivitis due to the Staphylococcus. Picture taken during exacerbation. Extreme sensitivity to Staphylococcus toxoid on intradermal test.

processes Only the Staphylococcus appears to fill both requirements in this re[illegible] Allergic staphylococcal conjunctivitis will be discussed in [illegible] in this chapter However it must be emphasized that n[illegible] [illegible] conjunctivitis may occur without the presence of or previous [illegible] what we consider pathogenic organisms Even nonpathogenic [illegible] bring about an allergic state in certain individuals and this [illegible] explain the occurrence of microbiallergic conjunctivitis where [illegible] non toxin producing *Staphylococcus albus* is found [illegible] many varieties of which elaborate both an erythro[illegible] hemolysins as well as various antigenic substances derived [illegible] them selves—such as M and T antigens and also P sub[illegible] [illegible] also be capable of causing allergic conjunctival reactions [illegible] experience does not indicate the necessary repeated exposure [illegible] noted above We have not encountered any instances in [illegible] to products of streptococci has resulted in conjunctivitis— [illegible] tious eczematoid dermatitis of the eyelids due to strep[illegible] occur on rare occasions (5), and many instances of endogenous uveitis appears to be due to such streptococcal allergy Potvin and Bo[illegible] (6) however in their monograph stated that ' allergic infectious blepharo conjunctivitis may occur from allergy to staphylococcal streptococcal and gonococcal products exotoxins as well as endotoxins but they admitted that difficulties exist in diagnosing allergic streptococcal conjunctiviti[illegible] Duke Elder (7) also referred to allergic streptococcal conjunctivitis Such entities if they indeed exist are admittedly rare

Although we have not had the opportunity to study such cases it has occurred to us that some instances of so called endogenous gonococcal conjunctivitis of a bygone era may have been allergic rather than metastatic in nature This is supported by our present concepts of uveitis and the characteristics of gonococcal iritis The allergenic substance is presumably gonococcal endotoxin Other chemical components of the gonococcus do not appear to be especially antigenic possibly because the infection stimulates little antibody formation due to its local character However the instillation of gonococcal extracts in the conjunctival sac may produce phlyctenules (8) It is possible that other forms of endogenous conjunctivitis such as have been stated to occur in bacillary dysentery as well as in Reiter s disease are also due to endogenous microbial allergy

The well known Calmette test occurring when tuberculin is instilled in the conjunctival sac of tuberculin positive individuals or animal may be noted as another form of conjunctival allergy to microbial product However, in a broad sense clinical allergic conjunctivitis on such ba[illegible] does not occur except in phlyctenular keratoconjunctivitis which is di[illegible] cussed in chapter 16

As far as is known the other bacteria that frequently cause conjunctivitis, such as the pneumococcus, *Moraxella lacunata* (diplobacillus of Morax-Axenfeld), *Hemophilus influenzae* and the Koch-Weeks bacillus do not cause allergic reaction. It may eventually be found that the allergenic properties of brucella products are responsible for allergic reactions of the conjunctiva. The pneumococcus has been shown to cause other ocular allergic reactions (9).

MICROBIALLERGIC CONJUNCTIVITIS DUE TO THE STAPHYLOCOCCUS

The contributions of Woods (10) and of Burky (4) have established that hypersensitivity to staphylococcus toxin is the cause of many cases of chronic recurrent conjunctivitis. Clinically these cases, as described by Woods, are characterized by dryness, absence of purulent discharge (Plate I, fig. 5), follicles, marginal blepharitis, reddened swollen margins of the eyelids, frequently slight secondary corneal changes, the isolation of a toxin producing staphylococcus from the conjunctiva and the presence of a high degree of cutaneous sensitivity to staphylococcus toxin. Positive cultures need not occur; sometimes, even when all the other criteria for diagnosis are present, such cultures show no staphylococci on repeated tests. In these cases the staphylococci have been eradi





FIG. 11. Microbiallergic conjunctivitis due to the Staphylococcus. Quiescent stage, minor symptoms. Note follicles in lower lid.

cited but the local hypersensitivity remains. Only desensitization by means of injections of Staphylococcus toxin or toxoid effects a cure.

Woods feels that the mechanism of the conjunctivitis begins with staphylococcal infection which results in tissue hypersensitivity. Subsequent fresh infections, even if the original infecting organism is eliminated, result in recurrences of the conjunctivitis. He considers that a reaction of more than three by three centimeters to an intradermal injection of one tenth of a cubic centimeter of a 1:100 dilution of staphylococcal toxin is evidence of such hypersensitivity. He has found that the toxin is not irritative to the normal skin or mucous membrane.

The Toxins of the Staphylococcus

The important role of Staphylococcus in the pathogenesis of many common external diseases was formerly unappreciated because early investigators did not differentiate pathogenic toxin producing strains from the ubiquitous nonpathogenic varieties to be found on cultures of the conjunctival and other mucous membranes, the eyelids and the skin. The fact that the Staphylococcus produced extremely potent exotoxins and other toxic products was demonstrated more than fifty years ago; however, these toxins received surprisingly little attention from anyone except the French until 1929 when Burnet's (11) fundamental paper appeared

This work is the basis of modern concepts concerning these toxins, as well as of the therapeutic use of staphylococcal toxoid and antitoxin.

Burnet's studies were in relation to an unfortunate episode that occurred in Bundaberg, Australia, in 1928, which of itself served to highlight the importance of staphylococcal toxins. Twenty-one children were given injections of diphtheria toxin-antitoxin, all taken from a single bottle (containing no preservative) which was later found to have been heavily contaminated with *Staphylococcus aureus*. Within five to six hours eighteen children developed severe toxic symptoms, including collapse and cyanosis; twelve died within approximately twenty-four hours. All who recovered, including the three free from any immediate symptoms, eventually developed abscesses at the site of injection. It was finally proved beyond any doubt that death occurred because of a large dose of an acutely acting toxic agent (toxin), not from infection. Burnet and Kellaway's (12) definition of what they consider a true toxin is "a dissolved inanimate substance capable of damaging living cells which when suitably injected into an animal provokes the appearance in the serum of an agent capable of neutralizing specifically the destructive effect of the toxin."

The more important toxins elaborated by toxigenic staphylococci may be listed as follows: 1) a soluble, filterable, thermolabile, apparently single exotoxin, causing skin and tissue necrosis, hemolysis, death; 2) leukocidin destroying leukocytes; 3) enterotoxin causing food poisoning; and 4) an enzyme (coagulase) clotting blood plasma. In addition, only toxins (free from filtrates) have been found to be lethal for rabbits. Staphylococcal exotoxin and leukocidin are antigenic, stimulating the formation of neutralizing antitoxin according to the law of multiple proportions. Toxoid, that is, attenuated toxin having the same antigenic properties, may be prepared by treating staphylococcus exotoxin with formalin or by other methods. These toxic products contribute to the pathogenicity of staphylococci. However, some pathogenic staphylococci produce little or no exotoxin, and nontoxigenic organisms apparently cause infection because of their invasive capacity.

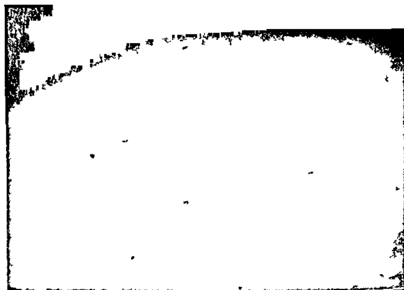




Fig 12 (*abo e*) Immed ate heal type of react on 15 minutes after ntra lermal injection of Staphylo occus toxoi l The marked reaction in this patient was nusu l

Fig 13 (*bel*) Delayed react on 24 hours after intradermal injection of Staph lococcu s toxoid While th s is tl e characteristic response in tl s pat nt it l ecame so extreme that it resembled a cellulit s

an index of immunity to Staphylococcus infection, the allergic reaction, which is of shorter duration, is uninfluenced by antitoxin and may be elicited by dilute toxin heated toxin or toxoid The intradermal reaction to dilute toxoid offers, within limits, an index of allergy to staphylococcal proteins and to other staphylococcal products While minor reactions to the injection of dilute toxoid or vaccine may be of questionable value it would appear that marked reactions are diagnostically significant of allergy (Figs 12 and 13) An allergic correlation of positive toxoid reactions with past or present staphylococcal infections has been found by Wagner and Maly (14)

We ourselves cannot agree with the view of some allergists that positive skin reactions to bacterial filtrates of themselves are of questionable diagnostic value It is our feeling that we should interpret these reactions as we do those of the tuberculin test A strongly positive reaction to a weak concentration indicates marked sensitivity and is diagnostically suggestive a mildly positive reaction merely indicates prior infection at some time or other in the past unless the reaction is recently acquired The patients who exhibit the greatest skin sensitivity generally are those with clinical evidence of low resistance to toxic staphylococci as evidenced by marked exacerbations when reinfection occurs

Diagnosis

Difficulties in assessing the importance of hypersensitivity to staphylococcal toxin and other products of this bacterium in the causation of chronic conjunctivitis arise from the fact that sometimes active infection is demonstrable while at other times none is found It has been shown by the work of Morax and Elmassian (15) and of Allen (16) that conjunctivitis may be produced experimentally by the local instillation of Staphylococcus toxin in persons apparently not hypersensitive to Staphylococcus products This would appear to be a direct toxic action a Allen s experiences with the beneficial effects of Staphylococcus antitoxin in corneal infections due to the Staphylococcus would seem to corroborate Moreover it has been established by the work of Thygeson (17) that infection with toxin producing staphylococci is a prime cause of blepharoconjunctivitis as well as chronic conjunctivitis in which allergy may play either a minor role or none at all Papillary conjunctivitis and a rather diagnostic superficial punctate keratitis of apparently toxic origin involving the lower half of the cornea are present Those cases with obvious ulcerative blepharitis or meibomitis are easily recognized where lid margin involvement is minimal diagnosis is less easy Basically this depends on the demonstration of toxigenic staphylococci by cultures of the lid

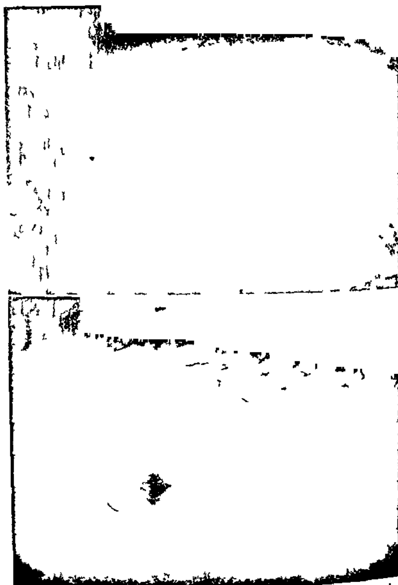


Fig 12 (above) Im[illegible] type of reaction 15 minutes after [illegible] injection of Staphylococcus toxoid The marked reaction in this patient was [illegible]

Fig 13 (below) Delayed reaction 24 hours after intradermal injection of Staphylococcus toxoid While this is the characteristic response in this patient [illegible] so extreme that it resembled a cellulitis

an index of immunity to Staphylococcus infection, the allergic reaction, which is of shorter duration, is uninfluenced by antitoxin and may be elicited by dilute toxin heated toxin or toxoid The intradermal reaction to dilute toxoid offers, within limits, an index of allergy to staphylococcal proteins and to other staphylococcal products While minor reactions to the injection of dilute toxoid or vaccine may be of questionable value it would appear that marked reactions are diagnostically significant of allergy (Figs 12 and 13) An allergic correlation of positive toxoid reactions with past or present staphylococcal infections has been found by Wagner and Maly (14)

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margins and conjunctiva and the finding of polymorphonuclear leukocytes and cocci on epithelial scrapings of the lid margins

How can we be sure then in what we call chronic microbiallergic conjunctivitis that it is not bacterial infection and the direct toxic action *of bacterial toxin that* is causing the conjunctivitis rather than allergy to this toxin and to other bacterial products? First of all we encounter patients suffering from chronic conjunctivitis in whom cultures reveal numerous colonies of nontoxin producing *Staphylococcus albus* These patients often manifest heightened skin sensitivity to toxin and often respond to toxoid and vaccine therapy Moreover even in persons in whom marked infection with toxin producing staphylococci exists extreme degrees of skin hypersensitivity are often demonstrable by minute injections *of Staphylococcus toxoid and other evidence strongly suggestive of al*lergy is noted (18)

A number of instances of such unusual hypersensitivity in the presence of strongly positive cultures have been encountered by us In one patient an intradermal injection of ten necrotizing units of Staphylococcus toxoid in the forearm caused such a severe local inflammatory reaction that the patient a truck driver could not use the arm for over a week Fever chills and malaise occurred for two days and he was unable to work His *year old ulcerative blepharoconjunctivitis perhaps the worst we had ever* encountered cleared completely in the course of time under intensive local non specific remedies (silver nitrate) and toxoid injections The *long* established value of silver nitrate in *blepharoconjunctivitis has been* ascribed to its coagulation of the superficial layers of the epithelium in that way causing death of bacteria It is possible that this drug may also neutralize the Staphylococcus toxin by some similar chemical reaction

This happened before the advent of the sulfonamides and antibiotics but other instances similar to this one have been noted since Sometimes even the most minute amounts of toxoid (one or two units) cannot be tolerated A patient with a most severe staphylococcal eczema of the eye*lids of ten years duration on whose conjunctiva* and lid margins were found innumerable colonies of toxin producing hemolytic coagulase positive *Staphylococcus aureus* recently demonstrated that this is not unusual *Intradermal injections of autogenous vaccine and Staphylococcus toxoid* gave marked immediate reactions Even injections of minimal doses had to be discontinued because on several occasions the patient developed transient acute arthritis of the fingers Symptoms due to *chronic chole*cystitis also became aggravated following these injections There could hardly be any question that in this patient a most exquisite allergy to the Staphylococcus and its products was present Later cultures of *the* gallbladder after its removal revealed *Staphylococcus aureus*

It would therefore appear that in repeated or long standing staphylococcal infections whether or not active infection is present some degree of allergy to staphylococcal products eventually plays a role of varying importance in the perpetuation of symptoms. According to Prigal (19) low resistance and allergy to staphylococci may be hereditary and familial. Even in patients in whom infection is obvious the eradication of the bacteria by intensive anti infective agents often does not suffice without treatment of this allergic component. It appears to be hardly a matter of increasing resistance by active immunization rather it is one of desensitization. The hypersensitivity is best treated by injections of Staphylococcus toxin or toxoid and vaccine preferably autogenous. As pointed out in chapter 13 where the subject is discussed from a different point of view vaccine is preferred in the treatment of sensitivity to bacterial products other than toxin.

Thus in summary the importance of Wood's contribution is particularly appreciated in those cases of chronic conjunctivitis in which diagnostic tests are essentially negative except for a high degree of skin sensitivity to Staphylococcus toxin or toxoid. These patients often show few if any bacteria on culture of the conjunctiva and not very many more occur on the lid margins. They often have periods of exacerbation of their complaints with some objective increase in the conjunctivitis but clinical improvement may require several months. We use toxoid because it is extremely well with Staphylococcus toxoid injections. We use toxin first in that it appears to readily available commercially. Toxoid differs from toxin in that it has been detoxified with formaldehyde and also in that it appears to have additional hemolyzing and dermonecrotizing factors.

Further evidence in favor of Woods concept may be obtained from patients with chronic conjunctivitis associated with infection of the paranasal sinuses by toxin producing staphylococci. Conjunctival cultures are generally negative. Skin tests may be definitely positive. Such conjunctivitis often responds to injections of vaccines and toxoid or to treatment of the exciting focus by either intensive antibacterial therapy or surgery.

Differentiation From Chronic Atopic Conjunctivitis

In the preceding chapter mention has been made of the difficulties that may arise in the differentiation of chronic atopic conjunctivitis from microbiallergic conjunctivitis due to the Staphylococcus. In table 3 an attempt is made to illustrate the differences between these two major forms of chronic allergic conjunctivitis.

TABLE 3

Differentiation of chronic types of allergic conjunctivitis

	Chronic Atopic Conjunctivitis	Microbiallergic Conjunctivitis Due to the Staphylococcus
History	Familial allergy frequent Other associated allergies	Familial allergy infrequent No associated allergies
Allergens	Pollens, danders, inhalants, foods	Bacterial products, mainly Staphylococcus toxin
Allergic response	Immediate	Delayed
Symptoms	Burning, irritation, and often severe itching	Burning, irritation, and often marked dryness
Discharge	May be mucopurulent	Watery, no pus
Lid margins	Usually uninvolved	May be swollen, possible blepharitis
Conjunctiva	May appear same in both types Often little objectively noted Sometimes edematous	May appear same in both types Papillary, but scattered follicles may appear Dry, no chemosis
Cornea	Generally not involved	May have superficial punctate keratitis involving inferior portion of cornea
Epithelial scrapings	Eosinophiles almost always found sooner or later	No eosinophiles
Cultures	Normal flora	Toxin producing staphylococci found, or normal flora
Intracutaneous Staphylococcus toxin or toxoid	Moderate delayed response	Marked delayed response, at least 3 x 3 cm., usually more, may have marked immediate response also, may get systemic reactions (arthritis)
Response to vasoconstrictors	Local use often affords considerable symptomatic relief	Generally no great relief

TABLE 3—continued

	Chronic Atopic Conjunctivitis	Microbiallergic Conjunctivitis due to the Staphylococcus
Response to antihistaminics	Oral use often affords marked symptomatic relief	Generally no relief at all
Response to cortisone	Local use usually affords marked symptomatic relief	Relief in some cases but not the rule
Best treatment	Elimination of cause	Staphylococcus toxin or toxoid injections

MICROBIALLERGIC CONJUNCTIVITIS DUE TO FUNGI

As noted in the previous chapter allergic conjunctivitis due to mold spores is not uncommon Essentially an inhalant form of allergy like pollen allergy, the allergic reactions these fungi arouse have many of the characteristics of the immediate atopic response Such conjunctivitis was therefore discussed as a manifestation of atopy

Other types of fungi of more pathogenic character cause allergy only after a primary infective focus has been established Here the mechanism is of the delayed tuberculin type The main ones of this group are the dermatophytes, such as Trichophyton and *Candida albicans* (Monilia) causing skin diseases Thus after a demonstrably infected primary dermatitis has occurred id reactions may appear elsewhere These id lesions reveal no fungi and disappear spontaneously when the original lesion is successfully treated In the eye such allergic reactions occur mainly as eczematous lesions affecting the eyelids (discussed in chapter 13) only rarely is the conjunctiva involved

Dermatophytids of the conjunctiva are indeed almost oddities Although Muende's case (20) was not the first reported it is easily the one most carefully studied and is most instructive The patient was a boy of ten years who suffered from a deep seated Trichophyton infection of the scalp At the onset an intradermal trichophytin reaction was almost negative Sixteen days after an epilating dose of x ray was given he developed a generalized trichophytid of the skin as well as an acute bilateral conjunctivitis accompanied by fever Smears of the conjunctiva revealed pus but no organisms A slight corneal infiltrate in one eye was noted a few days later but soon disappeared Both the eruption and the conjunctivitis gradually retrogressed in two weeks Eight days after the first eruption had disappeared another occurred but this time the conjunctiva was not involved At this juncture two days after the appearance

of the second trichophytid the trichophytin reaction was found to be strongly positive With local treatment both the scalp lesions and the second trichophytid of the skin disappeared in six weeks

This patient illustrated the variations that occur in allergy At the onset hypersensitivity was slight Later, allergy increased and a trichophytid developed—possibly due to the entrance into the blood-stream of fungus products (spores or mycelium or toxins) secondary to x ray or local therapy Such hematogenous spread from a primary focus has been demonstrated At this point as Muende states the trichophytin test became strongly positive

Peck (21) has followed a patient who similarly developed trichophytids of the skin and conjunctiva while under treatment for trichophytosis of the feet Cultures of the conjunctival secretion were sterile A trichophytin test was strongly positive When the original focus was successfully eliminated the allergic skin and conjunctival complications disappeared

Leszczynski (22) described a girl of fourteen years with trichophytosis *of the face involving the frontal region, nose, ears neck and left upper* eyelid with some conjunctivitis The evening of the day an injection of a small amount of trichophytin was given she developed fever, local reaction at the site of injection lichen trichophytique focal reactions of the skin and intensification of the eyelid lesion with marked reaction and edema of the conjunctiva characterized by hyperemia tearing and pain

This conjunctival exacerbation which he felt was a trichophytid Leszczynski described as toxic conjunctivitis, it was the subject of his short report It reminded him of similar conjunctival reactions in patients with tuberculosis treated by the Calmette method where alarming exacerbations occurred following the cutaneous reactions The skin and eye cleared completely in Leszczynski s patient three weeks after treatment

We agree with Muende that Milian and Lelong s (23) case of trichophytic keratoconjunctivitis was not on an allergic basis since there was a definite focus of infection in the inner angle and canthus itself

Since coccidioidin positive children may develop phlyctenules (24) it is possible that they may develop other manifestations of microbiallergic conjunctivitis *Such a possibility may also exist in regard to* histoplasmosis although phlyctenules are apparently not encountered in this infection

MICROBIALLERGIC CONJUNCTIVITIS DUE TO HELMINTHS

There is a good deal of evidence indicating that parasitic infestations may give rise to an *allergic state The antigenic nature of* helminthic products is well known The blood eosinophilia that occurs with parasitic infestations is suggestive of an allergic mechanism Skin tests utilizing

helminthic products as antigens are of value in the diagnosis of parasitic infestations Reactions similar to anaphylaxis have been elicited in dogs and guinea pigs by the initial intravenous injection of deproteinized extract of Ascaris Rupture of an echinococcus cyst may cause anaphylactic shock Morenas (25) has produced parasitic allergy to Taenia and Ascaris extracts by means of sensitization through the digestive tract comparable to that obtained by subcutaneous or intravenous injections

The experimental production of conjunctival allergy to intestinal parasites by Weinberg and Julien and by van Es and Schalk was mentioned in chapter 2 The former reported anaphylactic death in horses According to Morenas laboratory workers in this field especially those dissecting the parasites may contract allergic conjunctivitis from finger to eye contact Reactions similar to hay fever with conjunctivitis and asthma also occur A highly specific allergy to *Ascaris megalocephala* (horse) not *Ascaris lumbricoides* (human) was noted in one case Slaughterhouse workers also develop similar symptoms which disappear when such exposure no longer occurs

Asthma due to infestations with Ascaris Schistosoma and *Bothriocephalus latum* are noted by Urbach and Gottlieb (26)

At least two instances of recurrent allergic conjunctivitis related to Oxyuris infestation have been recorded Gotz s (27) case involved a patient with severe bilateral conjunctivitis and lid edema as well . vasomotor rhinitis in whom forty allergic skin tests were all negativ Eosinophilia of eight per cent suggested a search for parasites revealin Oxyuris Skin tests with this antigen gave a positive immediate whea response Effective treatment eliminating the intestinal worms brought about a cessation of the ocular and nasal symptoms When these recurred ome time later Oxyuris was found once again in the stools Complete cure eventually occurred after treatment of the intestinal condition

Morenas case (28) was essentially similar although the symptoms of very red irritated conjunctivae with swollen lids and paroxysms of sneezing were marked only in the morning He was able to follow the patient who had had Oxyuris infestation for about 15 years through long periods of remissions and recurrences to eventual cure The acute conjunctival and coryzal symptoms fluctuated with the intestinal infestation the crises disappeared permanently when the worms were finally eliminated

The role of verminiferous infestation in phlyctenular keratoconjunctivitis is discussed in Chapter 16

Urticaria and asthma have been reported (26) as rare complications of malaria disappearing with adequate antimalarial therapy The allergens responsible for the reaction are thought to be the breakdown pro

ducts of the merozoites released from erythrocytes during paroxysms Allergic conjunctivitis may prove to be another *manifestation of this* hypersensitivity

In summary, careful stool and blood studies would appear indicated in cases of long standing conjunctivitis where other clues as to etiology are all negative

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5

ALLERGIC DERMATOCONJUNCTIVITIS

Contact allergy of the eyelids and conjunctiva constitutes by far the most common form of allergic reaction encountered in ophthalmic practice It is generally caused by the local use of drugs, it can also be caused by cosmetics, articles of clothing, jewelry, animal or vegetable products plastics, or chemicals used in industry In those instances where the conjunctiva is the focal point of contact, as in the use of ophthalmic drugs, the allergic reaction generally begins as a conjunctivitis, soon involving the adjacent skin of the eyelids in a typical eczematous dermatitis The particularly apt term "allergic dermatoconjunctivitis" has been applied to this clinical picture Where the eyelid skin is the site of the primary contact, conjunctival allergy plays little or no role in the manifestations and an allergic eczematous dermatitis occurs without conjunctivitis This form of reaction usually is the result of exposure to cosmetics apparel, jewelry, metals, plants or chemicals, and is the most frequent cause of acute ocular eczema While basically the allergic mechanism is the same, only allergic dermatoconjunctivitis is discussed at this point, allergic eczematous dermatitis of the eyelids is discussed in chapter 12 From the major clinical points of view of clarity of presentation, recognition, differential diagnosis, and management, this division appears advisable

Allergic dermatoconjunctivitis, or contact allergy of the conjunctiva, almost always is due to an ophthalmic drug (1) Such a medicament does not cause a reaction on first contact, at least a week is required for sensitivity to develop Such sensitivity need not originate from conjunctival application but may result, for example, from systemic use of the drug Once the allergy is established and the conjunctiva exposed to the excitant, it requires hours (usually twenty-four to forty-eight) for its de-

velopment—unlike the reaction in atopic conjunctivitis where it is a matter of minutes Similarly it takes a number of days or a week after the offending substance is eliminated for the allergic inflammation to subside In contrast to the patient with acute atopic conjunctivitis who usually has both a familial and a personal history of allergy, an atopic background appears to play no role in allergic dermatoconjunctivitis All this conforms to the usual pattern of the delayed form of allergic response

To explain those instances where allergy has occurred the first time local application of a drug was made previously acquired sensitization from nontherapeutic agents of similar basic configuration such as dyes in colored foodstuffs has been hypothecated (2)

CLINICAL PICTURE

In the order of their appearance the following major diagnostic characteristics of allergic dermatoconjunctivitis are to be noted 1) severe itching of the eyes 2) papillary conjunctivitis 3) eczema of the skin of the eyelids and 4) conjunctival eosinophilia

The eczematous reaction (Plate II fig 1) is in almost all cases the outstanding feature of the condition Early mild cases may be characterized merely by slight dryness and thickening or abnormal wrinkling of the skin usually frank eczema (fig 14) occurs It is not necessary for both eyelids to be involved simultaneously Either the skin of the upper lid or that of the lower lid may be involved alone This often provides a clue as to the etiology When an allergic dermatoconjunctivitis is due to a drug especially to eye drops instilled in the lower cul de sac the earliest skin involvement may follow the usual paths of tear overflow (fig 15)—that is the canthi and the adjacent lower lid skin Allergy to ointments (fig 16) often first shows along the lid margins which are swollen and inflamed but do not exhibit the scales and ulcers seen in typical blepharitis On the other hand allergy due to cosmetics (fig 17) especially nail polish and hair tonic or rinses often first involves the skin of the upper lid

The conjunctival reaction (Plate II fig 2) may be severe Generally a mucopurulent discharge occurs resembling that noted in bacterial conjunctivitis The conjunctivitis is characterized by papillary hyperplasia isolated follicles may occur but they never dominate the picture the way they do in conjunctival irritation Furthermore the conjunctiva is diffusely and uniformly involved in the allergic inflammatory process In conjunctival irritation on the other hand the major involvement is localized to the area of contact usually the conjunctiva of the lower eyelid and the adjacent bulbar conjunctiva

The finding of eosinophiles or basophiles on epithelial scrapings is a very

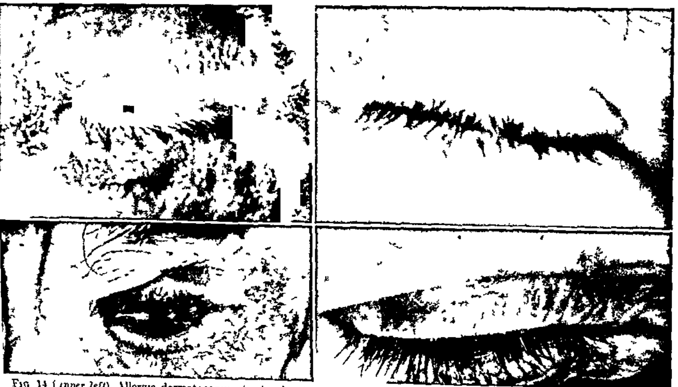


Fig 14 (upper left) Allergic dermatoconjunctivitis due to eserine Typical full blown picture after using drops for several months (Theodore Tr Am A Ophth 1954)

Fig 15 (lower left) Allergic dermatoconjunctivitis due to tetracaine Early stage following the usual paths of tear overflow

Fig 16 (upper right) Allergic dermatoconjunctivitis due to atropine ointment Early stage with major involvement of lid margins

Fig 1 (lower right) Allergy to hair-set Early stage with major involvement of the medial portion of the upper lid This was due to rubbing with fingers the scalp was uninvolved

valuable diagnostic aid in the recognition of allergic dermatoconjunctivitis They may not be present at the onset, but they usually appear if the reaction persists for several weeks

DIAGNOSIS

The diagnosis of allergic dermatoconjunctivitis when due to drugs is often easy The clinical appearance, the history, and the finding of eosinophiles in the secretion, followed by the beneficial effect of the elimination of the causal agent make a satisfying sequence of events The recognition of other causes of this type of contact allergy is often more difficult

It is important for the physician to differentiate allergic dermatoconjunctivitis from staphylococcal eczema (Plate II, fig 6) or infectious eczematoid staphylococcic dermatitis The latter condition may present a clinical picture resembling allergy very closely in fact the eczema that occurs while presumably due to the dermonecrotizing toxin of the Staphylococcus may actually represent an allergic response to Staphylococcus toxin Many unrecognized cases of this type of staphylococcic infection are treated for long periods of time as cases of contact allergy The intensive antistaphylococcic regimen including the use of toxoids and vaccines, which often is required to cure the condition is entirely different from that used in contact allergy Infectious eczematoid staphylococcic dermatitis as differentiated from allergic dermatoconjunctivitis, shows 1) blepharitis, often ulcerative 2) a drier more chronic type of papillary conjunctivitis with less discharge, 3) superficial epithelial keratitis involving the lower half of the cornea and seen best on slit lamp examination, 4) positive conjunctival and lid margin cultures showing numerous toxin producing staphylococci and 5) absence of eosinophiles in epithelial scrapings This is discussed in detail in chap 13

Patch Tests. Patch tests where the suspected substance is applied to the skin and covered by an innocuous impermeable material kept in place by adhesive are of value in contact allergy When positive a reaction generally appears after twenty four hours, sometimes the patch must be left on longer A negative patch test does not rule out the test substance as a causative agent because 1) under the circumstances of the test the mechanism producing the reaction may be lacking 2) the patient may no longer be sensitive 3) the actual sensitizer is not applied, and 4) only a local sensitivity is present and the site of skin tested is not sensitive (a not infrequent occurrence) It is important that the test material not be too concentrated as it then may act as a primary irritant giving a false positive reaction Thus in diagnostic testing for sensitivity to cosmetics it is better to apply the cosmetic daily in the way it is generally used because in normal use the uncovered cosmetic loses much of its substance by

evaporation Patch tests do not permit this evaporation, so that cosmetics which are harmless in actual use may cause positive reactions in patch tests

ALLERGENIC DRUGS

Many ophthalmic drugs are true sensitizers On occasion probably every drug used in the treatment of the eyes has resulted in allergic dermatoconjunctivitis in some individual In fact there is probably no drug or chemical in existence which everyone can use with impunity While nonprotein substances are in themselves not primary antigens it is believed that they form true antigens in the body by union with the host tissues These relatively simple chemicals known as haptens combine with body proteins forming conjugates that act as antigens The hapten confers specificity on the conjugate hence the allergy is directed against the hapten and not against the protein This explains why the substitution of a drug that is chemically similar to one that previously caused sensitivity in a patient is dangerous Thus after allergy to one sulfonamide has developed another sulfonamide is very likely to cause sensitivity As will be noted later in the chapter benzamine and other chemicals with para linked amino groups as compared to ortho and meta attachments are especially prone to cause contact allergies Unfortunately, very many of the drugs we use fall into that category

Sidi and Mawas (3) to whose extensive studies the reader is referred have recently published a statistical analysis of 312 cases of ocular contact allergy 132 due to therapeutic agents, 87 resulting from the use of eye drops and 45 resulting from the use of ointments Formerly most ocular drug allergies were the result of atropine and mercurials But ever since the introduction of the sulfonamides the para group of chemicals (sulfonamides and many synthetic local anesthetics) have been the major offenders, being responsible for about one third of all cases Nowadays of course the antibiotics also play an important role

In our experience allergic dermatoconjunctivitis is most frequently encountered in the groups discussed below

Local Anesthetics

It appears that every local anesthetic used for instillation into the eyes is a potential sensitizer Apparently every one in common use has been known to result in allergic dermatoconjunctivitis on occasion Often in the course of the treatment of external diseases of the eyes it is customary to instill local anesthetics as a preliminary to other medication It is surprising how frequently unsuspected allergy to these anesthetics is the reason for the inflammation becoming aggravated



Fig 18 Allergic dermatoconjunctivitis from tetracaine Same patient as fig 15 Papillary conjunctivitis eczema and conjunctival eosinophilia present *No follicles*

Of fifty seven cases of contact allergy due to medicaments reported by Jirasek and Schwank in 1954 (4) sensitivity to local anesthetics was found to account for more than half of them Tetracaine (Pontocaine) hydrochloride (fig 18) butacaine (Butyn) sulfate and Larocaine (3 diethylamino 2 2 dimethylpropyl p aminobenzoate hydrochloride) (5) are particularly likely to cause such allergies which are often very severe These drugs as well as procaine are of basically similar structure (para-amino groupings or modifications of it) and may cross react When allergy to one of them occurs the others should not be used The severity of allergy to anesthetic agents is illustrated by a case described by Ruedemann (6) His patient lost useful vision in one eye due to allergy from the repeated use of butacaine (Butyn) Later butacaine was used in the second eye for the removal of a foreign body with the result that almost complete loss of vision occurred in this eye as well

Dibucaine (Nupercaine) hydrochloride (7) and Diocaine cause far fewer allergies than those anesthetics mentioned above However cocaine hydrochloride phenacaine (Holocaine) and piperocaine (Metycaine) are far less likely to cause sensitivities and should be used whenever an allergic factor is suspected or where an allergy to other anesthetics has occurred Neither these drugs nor Xylocaine cross react as they are chemically unrelated to each other

Antibiotics

The tendency of penicillin to cause sensitivity is notorious The high incidence of local reactions (up to twenty per cent), especially when the drug is used in the form of an ointment, has tended to discourage its topical use Furthermore, allergies due to the ocular use of penicillin are among the severest encountered with any medicaments The high frequency of penicillin sensitivity may be related to previous sensitization of the skin by other fungus antigens, such as trichophytin, especially in adults Ocular reactions have also followed the use of intramuscular penicillin but they are generally not so severe Urticaria due to penicillin may have a different mechanism, similar to serum sickness Penicillin O may be tried where sensitivity to Penicillin G exists Once ocular allergy to the local use of penicillin has occurred, it may recur upon the parenteral use of the drug for other purposes as described by Wilson (8) and Egan (9) We have encountered a similar instance (Plate II, fig 5)

Streptomycin is another frequent and potent sensitizer Nurses often develop allergies after handling the drug and their eyes are frequently affected Dihydrostreptomycin while not really less toxic, appears less often irritating to the eye

Of the other antibiotics, personal experience would indicate that bacitracin is one of the least sensitizing however, we have encountered a number of relatively mild instances of allergy following its use It is possible that antibiotics derived from bacteria such as bacitracin are less allergenic than those derived from fungi as are most Thus sensitivities due to the local use of chlortetracycline (Aureomycin) (10), and oxytetracycline (Terramycin) occur more frequently Allergy to chloramphenicol (Chloromycetin) has been reported (11) but in our experience is extremely rare when the antibiotic is used as an aqueous solution

Originally neomycin appeared to cause very few local sensitivities although Baer and Ludwig (12) had reported an instance and we had also encountered contact allergy from this drug With the increasing and widespread use of neomycin in the more than fifty steroid antibiotic and antibiotic combinations now available for local use many unsuspected instances of local drug intolerance to these products may now be attributed to neomycin allergy According to Epstein (12a), who has observed twenty five proven instances of such reactions due to both ointments and solutions the allergy is of the dermal type (occurring in the dermis), rather than epidermal as in the usual contact allergies Most of his patients, who clearly could not tolerate mixtures containing neomycin and always improved when they were eliminated were negative on patch tests with neomycin However on intradermal tests (injections) with neomycin every one of these patients showed a positive delayed dermal (tuberculin type) reac

tion Epstein explains the clinical occurrence of neomycin allergy despite negative patch tests on the basis that the neomycin was more readily absorbed by the diseased skin to which it was applied than by normal skin.

So far polymyxin and tyrothricin do not seem to have great sensitizing propensities. However their increasing use in the various ophthalmic mixtures now available may result in contact allergies. The trend towards antibiotic mixtures for the purpose of greater activity over a wider bacterial spectrum makes recognition of the responsible allergen when contact allergy occurs increasingly difficult.

Sulfonamides

All sulfonamide drugs are potent sensitizers when used locally especially if the use is prolonged. Although sometimes very severe reactions are generally less serious than those encountered in allergies to the antibiotics and anesthetics. The newer sulfonamides such as sodium sulfacetamide (Sulamyd) and sulfisoxazole (Gantrisin) cause fewer allergies than the original drugs in this group such as sulfanilamide and sulfathiazole. Sulfirgamide (13) seems to cause very few allergies. As mentioned above many of the sulfonamides are parabenzamine chemicals, some contain pyrimidine rings which are present in many strongly antigenic drugs. The local use of sulfonamides may result in marked generalized hypersensitivity when they are taken systemically later on. On occasion preliminary systemic use of sulfonamides may so sensitize the ocular tissues that the first time they are applied topically exceedingly severe local reactions may occur (14).

Ophthalmic Alkaloids

The mydriatic alkaloids often result in sensitization. Conjunctivitis due to atropine is usually a typical allergic dermatoconjunctivitis. Eczematous dermatitis, papillary hyperplasia and a mucopurulent discharge containing eosinophiles and basophiles are all present. Under certain circumstances however atropine appears to act as an irritant and a follicular conjunctivitis develops without dermatitis and eosinophilia (Plate II fig 3). This manifestation will be discussed later (chap 6). Both scopolamine hydrobromide and homatropine give rise to a similar allergic dermatoconjunctivitis (fig 19). The miotic alkaloids on the other hand are rarely sensitizers. Prolonged use of pilocarpine (Plate II fig 4) or physostigmine (eserine) salicylate generally produces a follicular conjunctivitis with no dermatitis and eosinophilia which is due to drug irritation not to drug allergy. A true allergic dermatoconjunctivitis does occur in rare instances (Plate II figs 1 and 2). We have observed three instances of true allergy to each of these drugs and Holmberg (15) has reported



FIG 19 Allergic dermatoconjunctivitis due to scopolamine

three patients with pilocarpine allergy These cases, when associated with follicles, are explained by the fact that primary irritants may also be, or can become sensitizers Some instances, however, from which follicles are absent are due to typical allergic reactions Others have also reported cases (3 16) of pilocarpine allergy One of our patients, in whom all mi otics except pilocarpine caused irritative conjunctivitis, developed a dryness of both nasal passages from the continued use of pilocarpine in one eye only

Mercurials

All mercurial antiseptic agents tend to cause allergic dermatoconjunctivitis and this fact limits their prolonged use The inorganic salts are especially likely to do so, but even the newer organic mercurials are potent sensitizers Moreover, the fact that mercurials like sodium ethylmercurithiosalicylate (Merthiolate), nitromersol (Metaphen), mercury oxycyanide and phenylmercuric nitrate are frequently used as preservatives in ophthalmic solutions, and may thus be the unsuspected cause of allergies should also be remembered

Other Commonly Used Ophthalmic Drugs

Special attention should be called to certain frequently used drugs that may cause allergies on occasion These include ethylmorphine hydrochloride (dionin), Furacin, quaternary ammonium compounds like benzal-



Fig 20 Allergic dermatoconjunctivitis due to cortisone

konium (Zephiran) cetimide argyrol (mild silver protein) naphazoline (Privine) hydrochloride Paredrine (17) ephedrine adrenalin phenyl ephrine (Neosynephrin) zinc salts boric acid and even corticosteroids such as cortisone (fig 20) and hydrocortisone Iodine iodoform picric acid resorcin balsam of Peru ichthyol menthol and witch hazel when applied about the eyes have all caused allergic dermatitis Beryllium a component of the phosphors used in fluorescent lamp tubes (now less widely used) has caused such allergy (6)

Of special interest is the fact that antihistamines have produced so many contact allergies that the Council on Pharmacy and Chemistry of the American Medical Association (18) no longer approves of their use in the ointment form Sidi and Mawas (3) have called particular attention to sensitivities to these agents especially to Phenergan Allergy to antistine eye drops has been reported (19) Carr s excellent review on drug allergy (20) contains references to other antihistaminic sensitivities as well as to many of the other drugs discussed above

Ophthalmic Vehicles

Even if the active drug itself is harmless allergy may result from other ingredients in ophthalmic vehicles especially preservatives and ointment bases The 1953 regulation of the United States Food and Drug Administration requiring that commercially prepared eye solutions must be sterile and contain such preservatives as well as the new directions in the United

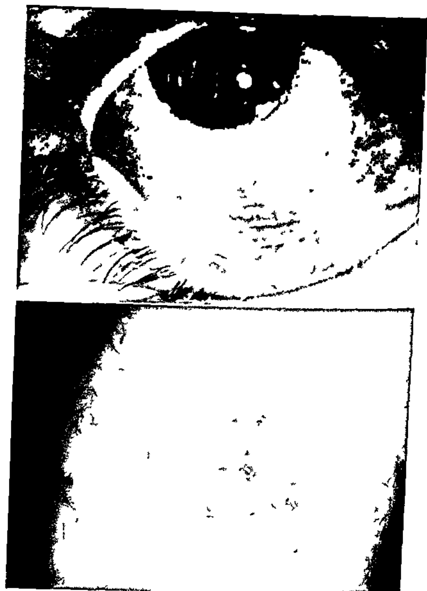


Fig 21 (*above*) Allergic dermatoconjunctivitis due to the *Merthiolate* used as a preservative in fluorescein solution

Fig 22 (*below*) Positive patch test to Merthiolate ointment in this patient (fig 21) Although patient removed patch in 24 hours reaction became so intense that extensive secondary cellulitis followed requiring sulfonamide therapy

States Pharmacopeia (1955) concerning the compounding of individual ophthalmic prescriptions, have thus highlighted a new source of allergic dermatoconjunctivitis. One of us, who was active in the campaign to enact these safeguards, and who originally pointed out their need, has long advocated chlorobutanol as a hypo-allergic as well as reliable preservative (21). Unfortunately, the fact that the use of chlorobutanol requires somewhat more care in the preparation of ophthalmic medicaments has prompted some manufacturers to use other preservatives which are often less effective against pathogenic organisms like *Pseudomonas aeruginosa* (*B. pyocyaneus*) and much more allergenic. Mention has already been made of the marked sensitizing properties of the mercurials. This is unfortunate because they are good antiseptics. Other commonly used preservatives like phenol derivatives, such as orthocresol, quaternaries such as benzalkonium which is allergenic as well as unreliable, and the esters of p-hydroxybenzoic acid all may cause marked sensitivities.

The importance of remembering preservatives as a possible source of allergy is well illustrated in the following case (figs. 21 and 22). A patient whose abraded cornea had been stained with fluorescein returned the next day with a most severe allergic dermatoconjunctivitis. It was suspected that the Merthiolate used as a preservative was the allergenic substance since fluorescein itself is rarely if ever a sensitizer. A patch test was so positive that the entire forearm became severely inflamed and swollen. The eyelid meanwhile after only the original instillation developed an almost gangrenous inflammation. Systemic Gantrisin was needed to control secondary infection. Had the fluorescein containing Merthiolate been used again the eye might have been severely involved and possibly lost.

Photosensitization may occur following the use of fluorescein. In one instance dermatoconjunctivitis occurred on exposure to sunlight after fluorescein was instilled in the eyes.

At least one instance of allergy to methylcellulose has been noted (22); the increasing use of this chemical in vehicles for ophthalmic solutions may result in more allergies from this product.

Allergies to ophthalmic drugs seem to occur more often when they are used in the ointment form than when they are used as solutions. It appears to us that even when the ointment itself is not allergenic the active principle such as penicillin is more apt to sensitize. Ointment bases themselves very often may result in allergies (fig. 23)—generally due to sensitivity to lanolin, petrolatum or oxycholesterol (Aquaphor). In such cases use of the active drug may be continued in another vehicle.

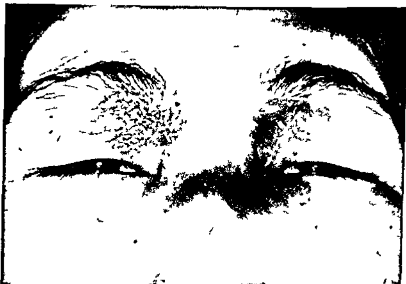


Fig 23 Allergy to ointment base Patient was not allergic to active drug itself but to the *base* (lanolin and petrolatum)

Prostheses

According to MacIvor (23) of one hundred persons fitted with plastic prostheses eight showed contact allergy, six resulted from plastic artificial eyes and two from partially exposed plastic implants These patients were relieved by the substitution of glass eyes Interestingly enough some of our observations concerning the pitfalls of patch tests were confirmed by MacIvor s studies Although all eight cases showed positive results when a small button of clear plastic was inserted in the conjunctival sac only two were positive when patch tested on the skin Two of our own patients could not tolerate plastic prostheses because of contact allergy

Forster and Dickey (24) reported marked dermatoconjunctivitis from a gold ball implanted in Tenon s capsule five years previously Skin patch tests were markedly positive Only the removal of the gold implant cured the condition

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DRUG IRRITANTS VERSUS SENSITIZERS

Reactive substances used as eye medicaments like other drugs and chemicals (1) may be divided into two classes 1) primary irritants and 2) mucosal and cutaneous sensitizers Some substances may act in both ways Primary irritants cause an inflammatory reaction only by direct action and just at the site of contact Inflammation occurs if the irritant is used in strong enough concentration or in sufficient quantity, for a long enough period of time Unlike an allergy the irritation may develop the first time the substance is used The conjunctiva and the very thin skin of the eyelids are both especially susceptible to the action of substances often not irritant elsewhere in the body Persons with dry skins are especially prone to react to dehydrating chemicals It is thought that the majority of occupational dermatoses are not allergic but occur in workers with anatomic or physiologic skin defects or on excess contact in those who do not take proper precautions (2) Primary irritants may in addition be sensitizers from the start or become sensitizers on intensive use This fact explains some types of conjunctival drug reactions that occur where an allergy is superimposed on a drug irritation

Mucosal or cutaneous drug sensitizers differ from irritants in that they act as true allergens Thus they do not generally cause reactions on first contact instead after approximately a week the entire skin or all the mucous membrane will react in a specific manner on further contact either at the original site or elsewhere These are the sensitizing substances that cause contact (delayed) allergy the type of conjunctival allergy just discussed as allergic dermatoconjunctivitis

IRRITATIVE CONJUNCTIVITIS

In chapter 5 it was pointed out that the cardinal characteristics of allergic dermatoconjunctivitis or contact allergy of the conjunctiva consisted of 1) itching 2) papillary conjunctivitis 3) eczema of the skin of the eyelids and 4) conjunctival eosinophilia As such the allergy is usually easily diagnosed The clinical picture of irritative conjunctivitis is quite different being in general nonspecific and rarely classical

The immediate reaction of the conjunctiva to irritants may vary from hyperemia to necrosis depending on the strength of the irritant Those irritants strong enough to cause severe immediate reactions are not germane to this discussion Conjunctival irritation due to ophthalmic medicaments first manifests itself by nonspecific chronic inflammation with a watery discharge Later in some instances proliferative changes and particularly in the case of alkaloids and related drugs the formation of follicles may then occur The conjunctival involvement is less diffuse and less uniform than in allergy often the area of most irritation the

6

DRUG IRRITATIONS OF THE CONJUNCTIVA

When the use of an eye medicament results in an untoward local reaction the physician is apt to consider the reaction as allergic and alter treatment on this assumption. The fact that such drug intolerance might be due to direct irritation of the conjunctiva rather than to a true sensitivity may be overlooked. Actually, it appears that irritative reactions to certain drugs are much commoner than allergies to these drugs. Such an assumption is especially true in regard to preparations of the alkaloid used in the treatment of glaucoma and uveitis. Drug irritations evoke a clinical picture quite distinct from that of drug sensitivities and usually may be easily differentiated. The importance of this distinction lies in the fact that in drug irritations the use of the same drug may be continued if it is prepared in a manner that insures no more irritation, whereas in allergies an entirely different drug must be substituted. In certain conditions such as glaucoma where intolerance to miotics is not uncommon it is sometimes not feasible to use another drug. On occasions such a situation may result in a decision to resort to surgery. Investigation of the cause of this intolerance may permit control of the tension by the continued use of nonirritating preparations of the same miotic if an allergy is not present. Before the concept of allergy was introduced drug intolerance was generally ascribed to some form of irritation. Now that the vast scope and many manifestations of hypersensitivity are fully accepted so many drug reactions are known to be due to contact allergy that not enough emphasis is being placed on the fact that drug irritations may occur.

negative with these low grade conjunctival irritants, stronger irritants may give positive patch tests. Epithelial scrapings may reveal mononuclear cells but no eosinophiles or basophiles.

This is different from the laboratory findings noted with severe chemical and vegetable irritants. Lime, ipecac, insect powders, indelible pencil, ricin, turpentine oil and probably many other substances result in an acute conjunctival reaction with massive eosinophilia ranging up to eighty per cent of all leukocytes (3). While such eosinophilia does not appear to be allergic as we understand the term, since it occurs after initial exposure and the clinical picture is essentially that of a burn, it is interesting to learn that some of these irritants do indeed contain allergenic substances. For example, it has been shown that extracts of castor bean contain not only ricin, a strong irritant and toxin, but allergenic products as well which may cause allergies after the ricin has been completely removed (4) (5). Moreover, according to Grabar and Koutseff (6), even ricin itself consists of a toxin, ricine, and a separate allergen, each having different chemical properties.

Follicular Conjunctivitis Due to Ophthalmic Drugs

It has long been recognized that physostigmine salicylate, pilocarpine and sometimes atropine may result in follicular conjunctivitis on prolonged use. Morax, in his classical monograph on the subject of follicular conjunctivitis (7), classified this response under the heading of "toxic follicular conjunctivitis," but stated that a sensitivity (allergy) caused this reaction. He believed that the purity, concentration, acidity, and sterility of the solutions played no role in the matter. Even at that time, however, there appeared to be a dissenting opinion. In 1925 Fleming (8) had observed that the incidence of follicles due to these three drugs had lessened considerably ever since he had employed a preservative in their vehicles, and thereby had checked bacterial contamination. The latter point of view coincides with our experience. It remained for Thygeson (9), however, to point out the fundamentally different reactions that occur with pilocarpine and physostigmine salicylate from that of typical allergic dermatoconjunctivitis. Thygeson felt that the follicular conjunctivitis due to the two drugs unaccompanied by the itching dermatitis and conjunctival eosinophilia typical of allergic conjunctivitis indicated a toxic follicular response and was not due to any allergy. Our own investigations on this subject were stimulated by this differential of Thygeson, but have led us to extend the hypothesis still further. It appears to us that the follicular responses observed with atropine, pilocarpine, physostigmine salicylate, diisopropylfluorophosphate (D.I.P.) and neostigmine, as well as those that may occur with others of this group, are the reactions to the formation of irritating degradation products by a group of drugs that are particularly



FIG 24 (*above*) Pilocarpine irritation involvement of the conjunctiva of the lower lid and lower bulbar region

FIG 25 (*below*) Pilocarpine irritation (same eye as fig 24) relative sparing of upper portion of the bulbar conjunctiva In allergy diffuse involvement always occurs in irritation when early it may be found

lower lid and adjacent bulbar conjunctiva bears the brunt of the involvement (figs 24 and 25) There is no preauricular lymphadenopathy Burning and irritation are major symptoms there is little if any itching The typical eczema of drug allergy does not occur Skin patch tests are

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This is different from the laboratory findings noted with severe chemical and vegetable irritants Lime ipecac insect powders indelible pencil ricin turpentine oil and probably many other substances result in an acute conjunctival reaction with massive eosinophilia ranging up to eighty per cent of all leukocytes (3) While such eosinophilia does not appear to be allergic as we understand the term since it occurs after initial exposure and the clinical picture is essentially that of a burn it is interesting to learn that some of these irritants do indeed contain allergenic substances For example it has been shown that extracts of castor bean contain not only ricin a strong irritant and toxin but allergenic products as well which may cause allergies after the ricin has been completely removed (4) (5) Moreover according to Grabar and Koutseff (6) even ricin itself consists of a toxin ricine and a separate allergen each having different chemical properties

Follicular Conjunctivitis Due to Ophthalmic Drugs

It has long been recognized that physostigmine salicylate pilocarpine and sometimes atropine may result in follicular conjunctivitis ... use Morax in his classical monogra... junctivitis (7) ... lar co... action ... of the ... centration acidity and sterility ... this re... ...yed no role in the matter Even at that time however there appeared to be a dissenting opinion in 1925 Elschnig (8) had observed that the incidence of follicles due to these three drugs had lessened considerably ever since he had employed a preservative in their vehicles and thereby had checked bacterial contamination The latter point of view coincides with our experience It remained for Thygeson (9) however to point out the fundamentally different reactions that occur with pilocarpine and physostigmine salicylate from that of typical allergic dermatoconjunctivitis Thygeson felt that the follicular conjunctivitis due to these two drugs unaccompanied by the itching dermatitis and conjunctival eosinophilia typical of allergic conjunctivitis indicated a toxic follicular response and was not due to any allergy Our own investigations on this subject were stimulated by this differential of Thygeson but have led us to extend the hypothesis still further It appears to us that the follicular responses observed with atropine pilocarpine physostigmine salicylate diisopropylfluorophosphate (DFP) and neostigmine as well as those that may occur with others of this group are the reactions to the formation of irritating degradation products by a group of drugs that are particularly

prone to deterioration unless prepared in solutions that will hinder or prevent such occurrences

We prefer to consider this type of drug intolerance a form of irritative reaction not a toxic one In fact it appears to us that follicular conjunctivitis of this type should be classified as irritative follicular conjunctivitis along with similar instances of follicular conjunctivitis due to other recognized irritants Repeated exposure to industrial irritants such as chemicals dusts and vapors results in irritative conjunctivitis, often complicated by the appearance of follicles Moreover while follicles could hardly be expected to occur in the more acute types *of chemical irritation* they have nevertheless been seen in artificial or self induced conjunctivitis In fact chronic irritative conjunctivitis due to repeated instillations of ipecac by malingerers has been at times confused with trachoma owing to the *numerous follicles that occur (10) In mild cases the follicles appear only* in the lower fornix in severe cases the upper lid conjunctiva is also involved The follicular responses to viral and bacterial toxins might even be considered as instances of toxic follicular conjunctivitis as here biologically derived toxins are probably active Perhaps the best example of this is molluscum contagiosum of the eyelids where the virus infection is entirely cutaneous and the conjunctiva is only exposed secondarily to extruded toxic viral products

Although both the terms toxic and irritative are only descriptive and do not indicate the ultimate mechanisms which at the cell level may be similar from a practical point of view the distinction is not an idle one If the reaction is a toxic one the drug must be discontinued unless in some way its toxicity can be blocked if a drug is an irritant or cell stimulant only when deterioration occurs preventing such degradation will eliminate the drug intolerance and permit its continued use We have observed clinically *as have others that the use of such offending drugs may often be continued* if these irritants are eliminated Such observations offer strong evidence in favor of the above hypothesis This does not mean that all cases of irritative conjunctivitis must exhibit follicles if the condition persists long enough *The occurrence of follicles as the result of any excitant depends* in large measure on the susceptibility of the person with a lymphoid diathesis to react in such a manner Thus while certain viruses will result in follicles in almost everyone other excitants (such as bacteria and fungi) as a rule do not do so but may do so in susceptible persons *Moreover in folliculosis* in spite of the absence of any excitant follicles may occur in the normal conjunctiva of children who show lymphoid hyperplasia elsewhere in the body Despite many statements to the contrary it appears that allergic conjunctivitis only rarely is characterized by predominating follicular involvement In a broad sense we have encountered it in only two types of

conjunctival allergy 1) in allergic reactions to atropine and physostigmine salicylate where an irritation preceded the allergy to both drugs and 2) in long standing chronic allergy especially the dry irritative conjunctivitis due to hypersensitivity to Staphylococcus toxin (11) where other factors may operate in causing the folliculosis However even in such cases follicles do not appear in significant numbers when compared to follicular conjunctivides of viral origin

PREPARATION OF NONIRRITATING OPHTHALMIC DRUGS

Drugs dispensed in ophthalmic solutions must be prepared in vehicles that will ensure their integrity over the period of use Most important of all is the maintenance of proper pH for that particular drug so that deterioration with formation of irritating degradation products will not occur While extremes of the pH range in themselves are irritating within reasonable limits of the normal pH of tears (6 5 to 7 0 (11a)) the pH of a solution is not of major consideration as far as the eye itself is concerned Phosphate buffers should be avoided as they may be both irritating and incompatible with certain alkaloidal salts Boric acid potassium chloride mixtures are advised The importance of isotonicity is debatable Since it is difficult to make a solution isotonic as well as buffered in all pH ranges when employing active drugs the pH should be the prime consideration since the buffer salts used automatically ensure an almost isotonic solution Exceptions to this general rule include methyl cellulose and distilled water Hypotonicity of a solution may be more irritating than hypertonicity

Sterility of ophthalmic medicaments (12) is desirable because in addition to the obvious danger of secondary ocular infection contamination even if nonpathogenic may bring about alteration of the pH deterioration of the drug and the formation of bacterial end products that in themselves may prove irritating Preservatives used to maintain sterility also must be carefully chosen *p* Hydroxybenzoic acid esters as well as benzalkonium chloride (cationic wetting agents) both frequently employed may be irritating Chlorobutanol is less likely to be an irritant Ointment bases themselves may be irritants

IRRITATION DUE TO ALKALOIDS AND RELATED DRUGS

Although the chemistry of the alkaloids is a very complex and not entirely understood subject consideration of the degradation products of these relatively unstable drugs suggests a rational basis for the fact that they as a group have such a definite tendency toward a specialized reaction when irritation occurs The most commonly used ophthalmic alkaloids and related synthetic drugs are considered from this point of view

Mydriatics

Generally atropine reactions are typically allergic however cases of atropine irritation occur (Plate II, fig 3) where a follicular conjunctivitis without dermatitis and eosinophilia is present It is felt that the basis for irritation is the fact that atropine itself a degradation product of hyoscyamine unless properly prepared will undergo further degradation to tropic acid and tropine (13) which is a strong alkali Final products are a group of esters known as tropeines All these substances are irritants Hyoscine (*l*-scopolamine) breaks down to atroscine which further degrades like atropine Homatropine breaks down to tropine and mandelic acid Irritation to homatropine is generally not encountered because the drug is usually not prescribed for prolonged home use

Miotics

As noted previously true allergy to pilocarpine is very rare—although *it does occur (fig 26) Pilocarpine intolerance is generally manifested by* nonspecific irritative conjunctivitis and less often (fig 27) by follicular conjunctivitis Pilocarpine dissolved in distilled water has a pH of 4 9 Constant use of this acid solution over a long period of time may of itself prove somewhat irritating Furthermore degradation of pilocarpine results in the formation of irritating end products such as acetic acid propionic acid ammonia and methylamine (14) which is a very strong base The optimum pH for pilocarpine solutions is 6 9 The relief of irritations owing to pilocarpine hydrochloride by substitution of the nitrate salts may occasionally be successful possibly because less degradation may occur Sometimes the use of another (freshly or differently prepared) solution of the same salts may be beneficial Generally, however the best remedy for pilocarpine irritation is to use a properly prepared solution We have noted on a number of occasions that such a solution will result in gradual disappearance of follicles and the relief of the irritative conjunctivitis Others to our knowledge have had the same experiences *Plate 2 figure 4 shows a patient who could not tolerate the usual prepa*rations of pilocarpine and developed a typical irritative conjunctivitis as a result Later properly prepared pilocarpine was well tolerated

Physostigmine salicylate is much more prone to result in a follicular conjunctivitis than pilocarpine Unless it is kept at a pH of 3 2 and an antioxidant such as sodium bisulfite is added rapid deterioration occurs with change of color owing to the formation by oxidation of rubreserine and methylamine (13) Because of its poor solubility rubreserine crystallizes in needle like crystals which may also act as mechanical irritants Further degradation depending on the rate of oxidation (15) results in either eserine brown or eserine blue (a strong base) All of these substances



Fig. 26 (*above*) Allergic dermatoconjunctivitis due to pilocarpine. Note the eczema and absence of follicles.

Fig. 27 (*below*) Pilocarpine irritation. Note the follicles and absence of dermatitis.

are chemical irritants Physostigmine salicylate in oil due to its increased stability is apparently less irritating than in distilled water as may be physostigmine salicylate ointment As noted in chapter 5 we have encountered cases of physostigmine salicylate allergy with dermatitis and eosinophilia In one since follicles were also present it was felt that at first a primary irritation occurred Later the irritant became a sensitizer a common occurrence and the allergy developed In another case no follicles were noted which indicated perhaps that irritation did not play a role

Diisopropylfluorophosphate is a definite chemical irritant In the presence of moisture hydrofluoric acid and probably elemental fluorine are formed Follicular conjunctivitis (fig 28) as a result of its use is not uncommon occurring like all the others in this group with the absence of dermatitis and eosinophilia The follicles in one instance disappeared after about one year despite continued use of the same commercial product *although conjunctival injection and symptoms continued Apparently* tolerance developed or else some lots are less apt to hydrolyze in the conjunctival sac In another patient (fig 29) using the drug in peanut oil a typical allergic dermatoconjunctivitis occurred with the absence of follicles This was shown to be due not to diisopropylfluorophosphate itself but to sensitivity to peanut oil Such a conclusion was inescapable in this particular patient even though it has been rather definitely established *that peanut oil is essentially nonallergenic—at least* when administered internally (16) The clinical reaction when a drop of peanut oil was instilled in the conjunctival sac as well as the occurrence of conjunctival eosinophilia were most striking

We have encountered a follicular conjunctivitis of the irritative type without dermatitis and conjunctival eosinophilia due to the prolonged use of neostigmine in a patient with glaucoma who previously had had a similar irritative follicular response to both pilocarpine and physostigmine salicylate He was later able to tolerate neostigmine from other bottle for several years until irritation again developed—this time however ele ired ly is lrol

ysis of neostigmine does take place it should result in the formation of dimethylamine a very strong base and 3 hydroxyphenyltrimethylammonium bromide Perhaps in the case described certain manufactured lots deteriorated more than others Intolerance to furtrethonium iodide has been noted to cause thickening of the conjunctiva especially of the lower fornix (17) and dacryostenosis owing to proliferative changes *There*



Fig 28 (*above*) Irritation due to use of diisopropylfluorophosphate Note numerous follicles and absence of dermatitis

Fig 29 (*below*) Allergy to peanut oil vehicle used for diisopropylfluorophosphate Papillary conjunctivitis (no follicles) eczema and eosinophilia were present

is little itching This would indicate an irritative process On the basis of its chemical composition which is similar in some ways to physostigmine salicylate and neostigmine it appears that methylamine would be one of the degradation products



FIG 30 Irritation from 20% solution of Mecholyl (methacholine) That this reaction was not allergic was proved by the fact that the patient could tolerate weaker concentrations

In summary, it appears likely that the basis for the irritative follicular conjunctivitis that is characteristic of the ophthalmic alkaloids is the formation of irritant degradation products This may largely be prevented by employing suitable means of preparation It is interesting to observe that all the miotic alkaloids and the synthetic miotics discussed above as well as methacholine (Mecholyl) (fig 30) and Carbachol (choline chloride carbamate) contain methylammonium radicals that apparently break down to methylamine or dimethylamine Whether this is of any special significance cannot be stated at the present time However when neurin choline and methylamine have been instilled in the eyes of rabbits conjunctivitis and superficial keratitis have resulted (18)

TREATMENT

The treatment of irritative conjunctivitis due to drugs is the use if possible of properly prepared solutions that will not result in degradation of the active drug into irritative end products Such solutions are commercially available Adjuvant use of cortisone derivatives or corticotropin may sometimes be necessary but is less valuable than in allergies Where a drug such as diisopropylfluorophosphate is the only effective one and must be used as supplied by the manufacturer, we have found that the patient may continue to use the drug for long periods of time without deleterious effects other than the persistence and the increase of the follicles As noted

above, sometimes the patient apparently becomes more tolerant to the drug irritants upon prolonged use, so that symptoms are less intense and the follicles may even disappear

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FIG 30 Irritat on from 20% solut on of Mecholyl (methacholine) T action was not allerg c was prove l by the fact that the pat ent co ild to concentrations

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depends first on arriving at a more or less definite etiologic diagnosis and second on the feasibility of such a separation In cases of bacterial allergy this is of course entirely impossible to accomplish Certain atopic reactions like allergic conjunctivitis due to animal dander or feathers can be eliminated readily but often economic or other factors make elimination of the cause out of the question in other air-borne allergies such as hay fever Even in contact allergies where removal of the cause is most readily accomplished difficulties often arise Sometimes in drug allergy the use of the drug is vital Similarly while industrial contact allergy may often be eliminated by hygienic protective methods such as filters and shielding devices when change in occupation is indicated circumstances usually make this economically and sociologically impossible

SPECIFIC DESENSITIZATION

There are two major indications for desensitization therapy in allergic conjunctivitis 1) atopic conjunctivitis due to air borne pollens molds or danders which can be neither eliminated nor successfully treated with drugs and 2) microbiallergic conjunctivitis due to the Staphylococcus Other types of conjunctival allergy are rarely if ever treated by this method Since most patients with atopic conjunctivitis do respond to drug therapy and since desensitization even if beneficial is often of only temporary value it generally is not performed unless other general manifestations of the allergy make it advisable to do so Such a decision and management are usually reserved for the allergist

Staphylococcus Toxoid

In the bacterial type of allergic conjunctivitis due to the Staphylococcus desensitization is often the only successful method of treatment since elimination of the cause is impossible and adjuvant therapy relatively ineffective Woods suggested desensitization with Staphylococcus toxin using 0 1 cc intradermal injections of a dilution of toxin that does not cause a large initial reaction He usually starts with 1 100 dilution but in more sensitive individuals uses the 1 1 000 strength The same process is repeated with the next stronger concentration until it too causes no reaction When a patient is able to tolerate 0 1 cc of a 1 10 dilution this dose is continued by weekly injections for six months to maintain desensitization and prevent recurrence of the sensitivity

We have obtained good results with the use of commercially prepared Staphylococcus toxoid Our regime has been basically the same as in the treatment of staphylococcal blepharoconjunctivitis and of staphylococcal eczema since the mechanisms involved are similar An initial intradermal injection of 0 01 to 0 02 cc serves as the diagnostic and therapeutic basis

7

TREATMENT OF ALLERGIC CONJUNCTIVITIS

Prerequisites for the successful management of allergic conjunctivitis are 1) recognition first that an allergy is present 2) the proper classification of the type of allergic conjunctivitis present, and 3) the discovery if possible of the sensitizing substance (1)

If one proceeds in this manner, considerable time as well as expense to the patient will be saved because it is often not necessary to determine the exact cause of the allergy in order to afford the patient relief The important thing is to have a well organized clinical approach to the subject based on an understanding of the mechanisms involved and the types of allergic conjunctivitis that may occur Even in those cases that present diagnostic difficulties the proper clinical understanding of this group of conditions will prove more valuable than blind reliance on sensitivity tests These of course are often necessary and sometimes vital to successful therapy but do require clinical evaluation as a governing factor as they may otherwise be misleading The therapeutic regime in allergic conjunctivitis should be as follows if the cause cannot be eliminated major reliance should be placed on nonspecific measures and drugs Desensitization is reserved for special instances An important principle especially in drug allergies is the avoidance in the treatment of any medicament likely to arouse new sensitivities in highly sensitized tissues which are not apt to be allergic to these drugs at other times

ELIMINATION OF THE CAUSE

The most effective therapeutic measure in allergic conjunctivitis is to eliminate the cause by either removing the offending antigen if possible or having the patient avoid it This is by far the best treatment but it

be present in ophthalmic suspensions of these drugs (3) Steroid solutions, such as prednisolone phosphate may eliminate this source of irritation which can occur on other bases as well (chap 6)

It is now generally accepted that the local use of corticosteroids where infection with the virus of herpes simplex exists usually results in the most serious sequelae due to the rapid extension of the corneal infection in an eye that appears relatively uninflamed due to the antiphlogistic action of the steroids A less appreciated danger from continued ocular steroid therapy is the precipitation of herpes simplex infection of the cornea by this medicament This is not rare in our experience and that of others (4) *In all persons prone to recurrence of herpetic infections in* general (such as cold sores) and particularly in those with a previous history of herpes simplex (dendritic) keratitis routine local use of steroids in the eyes is unwarranted and may be dangerous The herpes virus present in an inactive state in the tissues of such persons is triggered into activity by the local steroid therapy

The widespread use of steroids in combination with antibacterial agents has inadvertently accentuated these dangers Beguiled by the apparent basis for these combinations as promoted by their manufacturers who cite their wide range of effectiveness against both bacterial infections and allergies they are used with abandon not so much by ophthalmologists but by other physicians often for long and disastrous periods of time Since only ophthalmologists are equipped to recognize herpetic infections of the cornea warnings against the use of these products for such viral infection now common in the pharmaceutical literature provided are without any real meaning

Contamination of ophthalmic solutions by pathogenic bacteria as a cause of serious corneal infection was highlighted by the introduction of commercially prepared ophthalmic cortisone solutions (5) Due to lack of proper precautions gross infection with *Pseudomonas aeruginosa (B pyocyaneus)* occurred The particular vulnerability of cortisone and its analogues to such contamination became apparent This led to U S governmental regulations requiring the sterile preparation of all commercial ophthalmic solutions It must be remembered however when using corticosteroids that the danger of secondary infection through solutions infected *during usage* still exists, and that proper care must be exercised to avoid this

Other Medicaments

Other palliative remedies include local anesthetics vasoconstrictors and antiseptics all often used together

Anesthetics Cocaine still is a favorite because of its relatively low

are generally not needed Hydrocortisone or some of the newer steroid products are preferable to cortisone

Atopic conjunctivitis may be controlled by the use of local steroid three to five times daily Microbiallergic conjunctivitis is sometimes but not always alleviated by these agents

Topical instillation of steroid products for the treatment of allergic dermatoconjunctivitis is generally in itself, insufficient to block the allergy if the offending drug or chemical is not eliminated In milder drug allergies their local use may permit the continuance of the sensitizing drug especially if the offending medicament is stopped for a few days while the steroids are being used intensively After subsidence of the inflammation the use of weak concentrations of the allergenic drug along with steroids may sometimes be safe Usually however where any real degree of sensitivity exists and adequate use of the offending drug must be continued topical steroid therapy is not sufficient This is of particular importance in uveitis should allergy to mydriatics occur In such cases the systemic use of corticosteroids preferably corticotropin is indicated and is usually successful if used adequately A critical level of dosage must be maintained In a patient with uveitis who developed atropine allergy forty milligrams of ACTH daily allowed the continued use of atropine but twenty milligrams per day did not (2) During treatment a patch test positive before and afterward was negative

If through error a drug to which the patient is sensitive is instilled into the conjunctival sac immediate irrigation and repeated frequent use of hydrocortisone drops generally suffice to prevent the development of allergic dermatoconjunctivitis If the patient is highly sensitive an immediate injection of corticotropin is advised

Contraindications to the topical use of steroids Contraindication to the local use of steroids for conjunctival allergies include allergic and irritative reactions the triggering of infections with the virus of herpes simplex and the possibility of introducing bacterial infection by means of contaminated solutions

Allergic dermatoconjunctivitis from various steroid products has been mentioned in chapter 5 Such allergic contact reactions may be the result of the active ingredients of the medicaments themselves the vehicles and preservatives employed or the antibiotics and other antibacterial agents with which they are combined in manufacture such as neomycin

We have long noted that irritation to steroid preparation especially liquid suspensions appeared to occur much more frequently when these drugs were prescribed in concentrations of 1 5 or 2 5 per cent rather than in the weaker 0 5 per cent strength usually effective This may be explained in part by mechanical irritation from steroid particles shown to

be present in ophthalmic suspensions of these drugs (3) Steroid solutions such as prednisolone phosphate may eliminate this source of irritation which can occur on other bases as well (chap 6)

It is now generally accepted that the local use of corticosteroids where infection with the virus of herpes simplex exists usually results in the most serious sequelae due to the rapid extension of the corneal infection in an eye that appears relatively uninflamed due to the antiphlogistic action of the steroids A less appreciated danger from continued ocular steroid therapy is the precipitation of herpes simplex infection of the cornea by this medicament This is not rare in our experience and that of others (4) In all persons prone to recurrence of herpetic infections in general (such as cold sores) and particularly in those with a previous history of herpes simplex (dendritic) keratitis routine local use of steroids in the eyes is unwarranted and may be dangerous The herpes virus present in an inactive state in the tissues of such persons is triggered into activity by the local steroid therapy

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Other Medicaments

Other palliative remedies include local anesthetics vasoconstrictors and antiseptics all often used together

Anesthetics Cocaine still is a favorite because of its relatively low

index of allergenicity. It may be used in rather weak solutions, 0.25 to 0.5 per cent. Holocaine is also valuable. Tetracaine (Pontocaine) and others are more likely to cause sensitivities.

Vasoconstrictors. Epinephrine, Privine, ephedrine and Neosynephrin still have a very important place in the treatment of allergic conjunctivitis. In fact, they allay the acute symptoms of pollen allergies much more effectively and rapidly than any other local medicaments.

Antiseptics. Certain ones, notably those fatty acid derivatives which do not cause irritation or allergy, such as sodium propionate, often are useful in that they counteract secondary infection and also have some soothing effects. They may be safely used in bacterial infections occurring in allergic individuals in whom the antibiotics, sulfonamides, or mercurial antiseptics may result in new sensitizations.

SUMMARY OF TREATMENT

Atopic conjunctivitis. Where the fundamental treatment of all allergic *elimination of the cause cannot be accomplished, therapy* should be based on the following considerations: 1) because the reaction is an exudative response with vasodilation, vasoconstrictors used both locally and systemically give the most rapid immediate relief; 2) because histamine plays a role in the pathologic physiology, antihistaminics are useful when given systemically; 3) because it is a manifestation of the immediate form of allergic response, desensitization is often successful; and 4) blocking agents like the steroids used locally or systemically are valuable but not as dramatically so as the vasoconstrictors. In special instances adjuvants such as air conditioning are useful in pollen allergies. In chronic atopic conjunctivitis, where there is less vasodilation and edema, less emphasis is placed on vasoconstrictors. If the cause cannot be eliminated, treatment begins with topical steroids. Antihistaminics used orally are indicated. If necessary and possible, desensitization is attempted *by the* allergist. In severe cases systemic steroid therapy as well as systemic vasoconstrictors such as ephedrine are useful.

Microbiallergic conjunctivitis. The treatment of this entity requires *the use of toxoids and autogenous vaccines. Detailed use of these biological* agents has been discussed in this chapter as well as in chapters 4 and 13. Local medicaments are used symptomatically. Potent antibacterial agents are neither indicated nor effective.

Allergic dermatoconjunctivitis. The best treatment of drug allergy is to eliminate the offending medicament and to use, if necessary, another drug having a similar pharmacologic action. The drug substituted should differ as much as possible chemically from the original excitant because once sensitization to a drug is evoked, allergies to related drugs are more

prone to occur. The drug chosen should also be the least likely to sensitize of all the medicaments available for the purpose because when an allergy occurs many drugs ordinarily harmless to the patient may act as allergens. Furthermore, even in the absence of an allergy, if an allergic background or history exists, the choice of the drug initially used should be based on these criteria. Serious and permanent sequelae have occurred following the indiscriminate use of highly allergenic antibacterial agents. These could have been avoided by the use of other equally useful but safer medicaments. If it is necessary to continue the use of a drug that is causing contact allergy, the concomitant administration of sufficiently large amounts of corticosteroids or corticotropin (ACTH) systemically is advised. Sometimes the local use of ophthalmic cortisone will suffice, permitting the continuance of the allergenic medicament; however, a definite quantitative dosage factor exists in regard to these hormones and must be kept in mind. Local steroids are of value in expediting recovery in allergic dermatoconjunctivitis and should be prescribed along with elimination of the offending agent. If necessary, in severe reactions systemic steroids or ACTH may be given for the short period generally needed for improvement to occur. Antihistamines, both systemically and locally, have not proved valuable in our experience, in allergic dermatoconjunctivitis, nor should they on theoretical basis be expected to be useful.

In contact allergy of the conjunctiva due to agents other than drugs a similar therapeutic regime is indicated. Should the offending allergen be a cosmetic or other product for which a substitute is available, the cause is readily eliminated. Where an occupational allergen causes the reaction (as indicated earlier in this chapter) a change may not be feasible.

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8

VERNAL CONJUNCTIVITIS

the

ace

spring' conjunctivitis but of all the many names given to this baffling condition the term 'vernal' has become the one used universally. Although

of specially predisposed atopic individuals whose constitutions have been conditioned by a number of general organic factors

Because of this lack of a clear-cut etiology, the known facts concerning vernal conjunctivitis will be presented first leaving the speculative aspects to the latter portion of this chapter

HISTORY

According to Beigelman (1) the first recorded reports of the disease were of the limbic type (by Arlt in 1846 and later by Desmarres in 1855) Von Graefe was the first in 1871 to associate these limbic changes with the tarsal vegetations of the palpebral type The important contribution of Saemisch who established the condition as a disease entity and pointed out its periodicity giving it its name of 'vernal catarrh' was made in 1872 through the medium of a thesis by his student Brockhaus and amplified further by Saemisch himself in 1876 In 1903 Herbert's great contribution (2) that conjunctival eosinophilia was such a valuable diagnostic aid in

vernal conjunctivitis appeared Axenfeld's classical monograph in 1907 (3) summarized his findings and the literature up to that time so thoroughly as to put the disease near its present clinical and pathologic level In 1910 Trantas called special attention to the corneal complications of the disease Since that time the major themes for investigation have been the etiology and treatment Pascheff has made many valuable contributions Early American students of the disease include Gradle Jackson and Lehrfeld Beigelman has written an excellent and exhaustive monograph on vernal conjunctivitis it is undoubtedly the most authoritative reference work available at present

CLINICAL ASPECTS

Vernal conjunctivitis is a relatively rare disease the global incidence appears to be below one per cent of all eye diseases encountered Reported statistics, particularly the early reports must be reviewed with some caution because for one thing diagnostic criteria often were not sound enough a criticism that even today may be levelled at non-ophthalmologic reports of dramatic therapeutic results Furthermore variations in frequency from year to year in the same clinic are not uncommon Certain factors appear to play a definite role in the occurrence of vernal conjunctivitis and will be mentioned here Of themselves they tend to give leads concerning the basis of the disease as do special constitutional factors to be discussed These will be referred to again when the etiology of this baffling condition is considered

Geography

The basic importance of warm weather for the occurrence of vernal conjunctivitis is well illustrated in the increased incidence in warm climates Incidences of up to two per cent have been reported in the Mediterranean area—especially in Italy the Balkans North Africa and Egypt Similar findings are noted in India and in Mexico In Japan an incidence of three tenths per cent has been reported (4) In northern Europe a frequency of less than one tenth per cent has been the rule In the United States a similar variation occurs the probable figure in New York City is much less than one tenth per cent while in Los Angeles it is about 0 25 per cent (1) In warm climates the limbic form of the disease predominates in cooler countries the tarsal conjunctiva alone or in combination with the limbus is usually involved

Sex

Vernal conjunctivitis almost always affects boys rather than girls Beigelman (1) who summarized the literature up to 1950 found that of

3,172 patients, 77 14 per cent were male In Ahmuddin's (5) series 1,404 were male, 467 female Our own experience would indicate an even higher male predominance—certainly between the ages of five and ten years This observation is confirmed by the statistics of Sakic (6) It appears, however, that after puberty the incidence is about equal in the two sexes All this would suggest a hormonal factor, which will be discussed later

Age

Vernal conjunctivitis is a disease of childhood The usual time of occurrence is from six to twenty years of age, according to Ahmuddin fifty-nine per cent of the patients were between eleven and twenty years old It rarely occurs after the age of 30 Botteri (7) reported the earliest onset, in a month-old boy Although this author himself did not examine the baby until he was two years of age, when he clearly had a full-blown vernal conjunctivitis, the child's father, a physician, who was himself still suffering from active symptoms of the disease, had recognized both symptoms and signs at the end of the first month of the child's life Interestingly enough, both the father and his brother had not developed vernal conjunctivitis until puberty Jackson (8) is credited with reporting the latest known onset, in a woman who apparently first developed the disease at the age of seventy-five It recurred each August for the next three years with palpebral, but not limbic, involvement A male patient of Pfluger's first manifested palpebral vernal conjunctivitis at the age of seventy-four (9)

Race

Colored races, especially the Negro race, appear particularly prone to the limbic form of the disease Palpebral involvement appears to be rather rare in such individuals

Familial Incidence

In a significant number of instances, vernal conjunctivitis occurs in two or more members of a family, often in a parent and child In at least fifty per cent of all patients an allergic background—that is, a history of allergy in the family—is noted Our own personal experience indicates an even higher percentage

Personal History of Allergies

At least half of all patients with vernal conjunctivitis suffer from other ... hay fever, asthma, and ... and molds The im- ... chapter

SYMPTOMATOLOGY

While symptoms in vernal conjunctivitis may be very slight at the onset of the disease once the condition is firmly intrenched they can become intolerable The most common and perhaps the most important symptom is itching Without this being present the diagnosis must always be questioned The intensity of the itching does not always parallel the objective changes Indeed some of the rudimentary cases are far more troublesome than those with giant vegetations as well as the early ones Itching is not necessarily pathognomonic of the disease While it may occur in any type of conjunctivitis allergic conjunctivitis is generally the major differential In hay fever itching may occur at any time of the day whereas in vernal conjunctivitis it appears to be more pronounced toward the end of the day

Photophobia is far less important as a complaint, but it is frequent and sometimes may dominate the clinical picture Less important complaints include a sensation of the presence of foreign material burning and lacrimation

The role that corneal epithelial lesions play in the causation of these symptoms has recently been stressed by several authors Gundersen (10) thinks conjunctival itching is always allergic and that in vernal catarrh it might be due to keratitis epithelialis disseminata as he finds it always present when the disease is active

OBJECTIVE FINDINGS

Vernal conjunctivitis is a *bilateral* affair However on rare occasions involvement of one eye may precede the other by a considerable period of time Some reputedly unilateral cases have been reported and we ourselves have encountered one instance Such cases are exceedingly rare

There are two main forms of the disease generally recognized 1) the palpebral and 2) the limbal In a significant percentage of patients a mixed type occurs where both lid conjunctiva and cornea show changes In addition rudimentary and atypical varieties are seen Ahmuddin (5) believes that a third major type of vernal catarrh which he calls the irritative form exists

Palpebral Form

The palpebral form of vernal conjunctivitis is practically always limited to the tarsal conjunctiva of the upper lid (figs 31 and 32) While there may be a minor extension of the process upward the fornix is almost never involved The tarsal conjunctiva of the lower lid only rarely shows the typical vegetations characteristic of the condition (fig 33) When such involvement occurs it indicates great severity of the disease Once in a great while the plica semilunaris is thickened and gelatinous but it is not involved most of the time



Fig 31 (*above*) Vernal conjunctivitis palpebral form involvement of the upper lid conjunctiva with a number of very large giant vegetations and marked pseudo-membrane

Fig 32 (*below*) Vernal conjunctivitis palpebral form diffuse smaller fleshy vegetations resembling acute trachoma



vegetations occur on the lower lid (rare) it indicates great severity of the process

At the onset there is general hyperemia followed in a few weeks by diffuse tissue hyperplasia. The conjunctiva becomes thickened and assumes a bluish white "milky" appearance. While the gross appearance is still that of a smooth surface, slit lamp study will reveal the presence of minute papillae each with a central small perpendicularly directed blood vessel which stands out against the increasingly opaque tissue; these were erroneously believed to be diagnostic "blood points." The condition may not progress beyond this stage, which is still considered the abortive form. Usually, however, the formation of the classical excrescences occurs. These vegetations are the well known hard flat papillae of varying—sometimes giant—size, which assume irregular polygonal shapes and give the characteristic "cobble stone" appearance (Plate I, fig. 6). Despite their size and their sometimes round shape these firm vegetations are not to be confused with follicles; they are papillae. The vegetations are most numerous near the proximal border of the tarsus with relative sparing of the area adjacent to the lid margin. The largest vegetations appear in the temporal portion of the tarsus. Sometimes the vegetations become so large as to damage the cornea mechanically. Slight ptosis due to the thickening of the upper lid is common.

The bulbar conjunctiva rarely shows any significant degree of involvement. Among the changes that occasionally may occur are newly formed vascular networks, raised yellowish gelatinous lesions, smaller vascular

conjunctival thickening (goose skin appearance) polyp[illegible] pseudopterygium and increased pigmentation in dark skinned individuals

Only in the rarest instance is the conjunctival fornix involved Changes in the semilunar fold while most uncommon have been seen more often

The discharge Associated with the conjunctival findings is a most characteristic discharge While early in the course of the disease there may be relatively little secretion concomitant with the appearance of large vegetations a definite discharge appears This is generally a ropy thick creamy white fibrinous pseudomembrane which may be peeled off the surface of the conjunctiva without any bleeding The stringy tenacious character of the secretion resembling chewing gum is a valuable diagnostic aid In milder cases a thin pseudomembrane is the rule Eversion of the upper lid and exposure of the under surface for several minutes will result in the *formation of a pseudomembrane* if it is not previously present Massage of the closed lids also aids in its formation Hot water dionin and even the heat of a slit lamp or camera lights (fig 34) will produce the same results The secretion is markedly alkaline a pH as high as 9 0 has been noted

The secretion is especially remarkable for the large number of eosinophiles it generally contains For this reason epithelial scrapings or secretion smears are of great diagnostic value Masses of eosinophiles are often found If the process is hyperacute myriads of eosinophilic granules which have escaped from ruptured eosinophiles may be seen It is probable that these eosinophiles arise locally in the conjunctiva itself rather than having a hematogenous origin Such extramedullary production of eosinophiles appears to occur on the basis of transformation of mucosal cells



Fig 34 (*Right*) Vernal conjunctivitis production of [illegible] ... an often useful diagnostic procedure

in other portions of the body such as the gastrointestinal tract (11) A similar mechanism might be postulated as operating in the conjunctiva in vernal catarrh Basophiles or mast cells also occur in significant amounts in the secretion They appear to increase in number during periods of remission (12)

The Bulbar or Limbal Form

In vernal conjunctivitis basically the same processes occur in the pericorneal region as in the tarsal conjunctiva After the initial period of simple hyperemia tissue proliferation occurs resulting first in opacification at the limbus which may be either focal or general This change is not especially diagnostic it is observed in trachoma eczematous (phlyctenular) conjunctivitis and other forms of conjunctival disease The second phase of the limbal process is thickening with the formation of the classical limbal lesions (fig 35) Usually these appear as one or more discrete gelatinous elevations yellow to gray in color situated generally in the palpebral fissure Sometimes the elevation is of a more confluent type (fig 36) forming a concentric rampart which is often massive There is usually no surface ulceration of these excrescences They usually do not stain with fluorescein The adjacent conjunctiva is injected the same characteristic vascularization consisting of perpendicular branches from the deeper vessels noted in the palpebral form is present

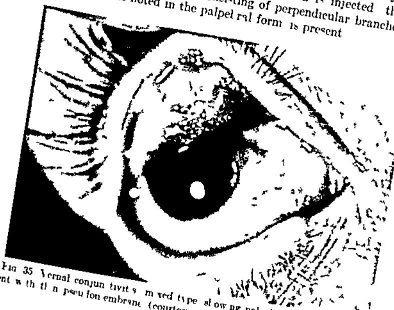


Fig 35 Vernal conjunctivitis mixed type showing palpebral and [illegible] involvement with [illegible] pseudomembrane (courtesy of Clay Adams Co)

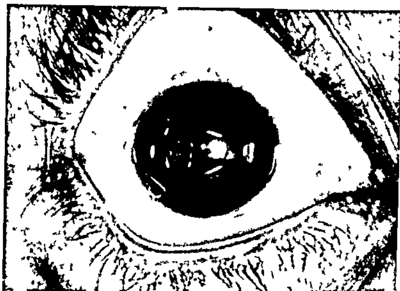


Fig 36 Vernal conjunctivitis limbal form involving the entire circumference of the cornea The eye appeared superficially uninflamed

The limbal excrescences are sometimes capped by white points—known as *Trantas points or spots* because of their exhaustive study by that investigator Actually they were first noted by Horner These ephemeral spots vary from pinpoint to pinhead in size, and are made up of degenerated eosinophiles and epithelial cells They are pathognomonic of the disease as they occur only in vernal conjunctivitis

Cystic spaces at the limbus may be noted Marginal pits or transparent depressions at the limbus have been described by Trantas as foci of regression of limbic lesions

The "Irritative Type"

In Alimuddin s (5) huge series of 1871 cases of vernal conjunctivitis recently reported from Pakistan he found that thirty one per cent of these patients manifested a somewhat different form of the disease Despite the characteristic symptoms of photophobia itching and epiphora the conjunctiva remained healthy A slight pericorneal flush as in early iritis was present with engorgement of the pericorneal vessels and marked increase in the aqueous veins This picture might recur summer after summer without hypertrophy ropy discharge or a milky appearance of the conjunctiva Epithelial scrapings of the conjunctiva revealed three to five eosinophiles per field Complete cure occurred in thirty per cent of

this irritative form of vernal conjunctivitis, another thirty per cent became limbal in character

Whether this clinical picture deserves special classification or represents only an intermediary or "abortive" stage of the disease, will require further evaluation Any opinion offered by an observer with access to such vast clinical material must be respected

Corneal Lesions

In addition to affecting the conjunctiva and the limbus vernal conjunctivitis involves the cornea itself in approximately half of all cases Such involvement, until relatively recently, did not receive the emphasis it deserves The changes noted are often valuable as both diagnostic and prognostic aids They may be overlooked for a variety of reasons First, in truly severe vernal conjunctivitis it is often not easy to obtain from the little patient the cooperation necessary to perform a satisfactory corneal examination—especially with the slit lamp microscope Second while the corneal changes often are a major source of the patient's complaints such as itching tearing and photophobia, at other times they may be found in relatively comfortable patients whom we might not examine too carefully Furthermore corneal involvement especially of the milder type may be transitory in the same patients and thus missed While these corneal lesions are in the main not too severe and generally disappear with the improvement in the disease as long as they are present they may cause serious visual diminution as well as discomfort On occasion but fortunately only rarely the involvement is so severe that permanent serious visual loss ensues

It is convenient to divide these corneal lesions into two classes 1) those occurring as direct extensions of the limbic and conjunctival disease and 2) those in which there appears to be no such direct extension Extension of the conjunctival process may result in a raised fleshy or gelatinous crescentic area occurring superiorly Lesions of this type are usually well tolerated by the patient Flatter pannus like formations located in the upper cornea are also encountered While generally thin, they may become well vascularized thus simulating trachomatous pannus A fibrovascular pannus which does not involve the limbal conjunctiva and sometimes develops concentrically has been described by Paschell (13) Direct invasion of the epithelium by vegetations usually is limited to the periphery of the cornea On rare occasions however the vegetations may extend over the entire cornea destroying Bowman's membrane in their progress Such cases of malignant vernal keratoconjunctivitis may leave serious opacities

The basis for those corneal lesions that do not appear to arise by direct extension from the conjunctival process is not clear It is believed that some of these may be toxic, or possibly nutritional in origin while a second group appears definitely dystrophic in type The frequently encountered yet often overlooked superficial epithelial lesion known as keratitis epithelialis vernalis (14) falls into this first toxic category The entire cornea may be involved but generally the keratitis is limited to the upper half The surface of the cornea looks as if flour has been sprinkled over it On biomicroscopy fine punctate lesions are seen staining often with fluorescein The lesions may cause temporary visual impairment Superficial epithelial keratitis is particularly common in the palpebral form of vernal conjunctivitis occurring in at least twenty per cent of all patients Removal of the tarsal vegetations often results in great improvement in the keratitis With the use of corticosteroids especially systemically superficial epithelial keratitis disappears most dramatically as soon as the earliest symptomatic improvement occurs often within a day or two after treatment has begun This serves as a useful objective index of therapeutic efficacy

Corneal ulcers of a superficial type having a subacute course are by no means an uncommon complication of severe vernal conjunctivitis They appear to be related to the presence of large palpebral vegetations and may respond only on the removal of such tarsal excrescences Secondary infection may of course supervene so that antibacterial measures are often valuable in these cases

Sub epithelial punctate lesions also occur occasionally especially in the limbal form near the corneal periphery These have a chronic course

The most common dystrophy that occurs is pseudogerontoxon which resembles true arcus senilis This may be complicated by degenerative changes breaking down to form ulcers The involvement may be irregular in width and not as sharply demarcated as an arcus senilis it is however annular and does have a narrow zone of transparent tissue separating it from the limbus Pseudogerontoxon is a valuable diagnostic finding which incidentally is one of the few manifestations of the disease to remain permanently as evidence of previous vernal conjunctivitis

Other late dystrophic corneal complications of vernal conjunctivitis include changes in curvature causing greatly increased myopic astigmatism and softening to the extent of developing of keratoconus (fig 37) and keratoglobus

Periodicity

Definite history of recurrent conjunctivitis occurring during warm weather and being relieved in cold weather is so classical for vernal con

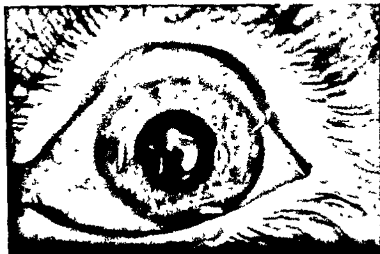


FIG 37 Vernal conjunctivitis keratoconus with central corneal opacity (same patient as fig 32) Numerous corneal reflexes due to irregular astigmatism are visible

junctivitis that one must suspect the condition whenever such a story is elicited In the temperate zones the usual onset occurs in the spring or early summer and abates gradually with the cool weather in the fall During the winter the symptoms of itching lacrimation and photophobia usually disappear entirely except in severe cases There is also considerable objective improvement with the disappearance of the limbal proliferations, but the palpebral vegetations almost always remain In the torrid zone where such clear cut delineation of seasons does not occur the seasonal incidence of vernal conjunctivitis is different

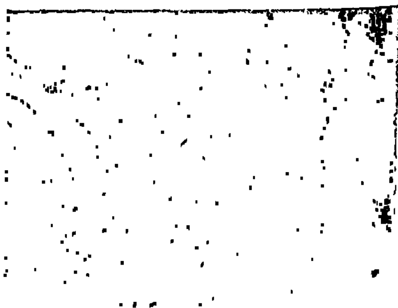
We have encountered numerous cases of soldiers who previous to their being stationed in Florida, had little or no vernal conjunctivitis In this sub-tropical climate typical symptoms developed during January and February Similarly a patient from the Argentine had had symptoms of vernal conjunctivitis for the previous ten years in the months of November December and January Arriving in Europe in October he was free all winter but in June developed severe symptoms thus illustrating the dependence of vernal conjunctivitis on the warm season

There are however a number of cases on record where exacerbation of the disease occurred in the cool months of the year There are still other cases where little or no relief in symptoms occurred during the winter Of course most of these perennial cases all were noted in warm climates but they can occur in cooler zones There are still other cases where remissions occur for one or two seasons after which the symptoms recur

breaks down into minute fragments which are then carried away Finally, a complete return to normal occurs

The milky, bluish color of the conjunctiva in vernal conjunctivitis is due to these connective tissue changes The opaque hyalinized tissue prevents the capillaries from imparting the usual pink color to the conjunctiva Only the larger, perpendicular blood vessels are visible as the "blood points" The enormous overgrowth of the fibrous tissue explains the cartilaginous consistence of the vegetations of vernal conjunctivitis

Changes in the conjunctival epithelium. The epithelial proliferation constitutes a spectacular feature of the histologic picture in advanced vernal conjunctivitis In those parts of the conjunctiva in which vegetations almost never develop, such as the fornix or semilunar plica the layers, normally numbering two or three, are increased more or less uniformly to six to eight layers or more Over the excrescences a similar hyperplasia occurs, but at the flattened tops of the larger vegetations the epithelium becomes thinned and sometimes keratinized In between the papillae, however, tubular proliferations of columnar epithelium occur (fig 41), reaching thirty to forty layers of cells, extending deep into the submucosa but never penetrating the tarsus Such nests of cells when seen on section often give the appearance of epithelial tumors The simultaneous degeneration and proliferation combine to produce a characteristic



of

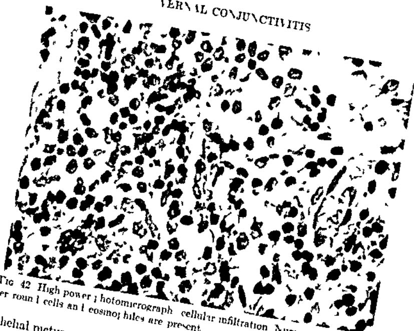


FIG 42 High power photomicrograph cellular infiltration Numerous lymphocytes other round cells and eosinophiles are present

epithelial picture—that is transformation of type as noted by Beigelman (1) The ultimate destruction of some of these epithelial cells results in the formation of epithelial cysts

Cellular response The cellular infiltration is characterized by masses of lymphocytes, plasma cells and fairly numerous eosinophiles (fig 42) In addition histiocytes mast cells polymorphs and fibroblasts are found in varying amounts In advanced cases the major accumulations of cells occur deep in the stroma and are separated from the epithelium by heavy bundles of hyalinized connective tissue The infiltration never extends to the tarsus

Lymphocytes These occur singly or in large masses but genuine follicles are rare In the regressive stages they diminish in proportion to the improvement

Plasma cells Plasma cells appear later than lymphocytes and are subject to striking seasonal changes During periods of exacerbation they are found in large numbers during remissions they degenerate and disappear

Histiocytes These cells often actively phagocytic are widely encountered especially in the substantia propria Large mononuclears are particularly abundant in regressive stages wherever cellular or fibrillar debris occurs

Eosinophiles Eosinophiles are unquestionably the most characteristic

cells of vernal conjunctivitis even though they do not stand out numerically. Their early appearance and their constancy throughout the course of the disease make them of prime importance as they can be identified in any portion of the affected conjunctiva. Actually, the proportion of eosinophiles to other leukocytes is much smaller in the substance of the conjunctiva itself than in the conjunctival secretion. They are particularly apt to appear in the superficial layers near the epithelium which they readily penetrate. Occasionally they are seen in the process of migration through the walls of the blood vessels. During remissions eosinophiles do not diminish in number materially.

Mast cells. The most striking feature of the mast cells is their appearance in great numbers during remissions, this, as Axenfeld and Rupprecht pointed out (26), is just the opposite of the behavior of the plasma cells. Mast cells are even more intimately related to the vascular system than are eosinophiles and display a great migratory tendency penetrating the epithelium.

Neutrophiles. Polymorphs are apt to be more conspicuous in the early phase of the disease.

Fibroblasts. Tissue fibroblasts do not appear in such large quantities as they do in trachoma and numerically are not in proportion to the hyperplasia of the connective tissue.

The Cornea

Changes of an essentially similar nature occur in the limbal form of vernal catarrh. Here, however, the three basic pathologic findings are emphasized differently. The most outstanding finding is the epithelial proliferation which greatly overshadows the connective tissue and hyaline degeneration. The enormous epithelial overgrowth extends downward forming plugs and nests resembling epitheliomas. Usually Bowman's membrane is left intact although in severe cases it may be destroyed. The cellular infiltration consists of the same types of cells as those found in the conjunctival lesions.

Extensions further into the cornea are basically of the same character again modified by the corneal terrain. Fibropapillar hyperplasia with local eosinophilia generally is noted. In vernal pannus newly formed vascularized fibrous tissue dominates the picture.

In dystrophies of the corneal epithelium examination reveals degenerative changes of various types, necrosis, granules, vacuolization and swelling occurring in the epithelial cells are found.

The relative unimportance of the fibrous tissue changes in the limbic as compared to the conjunctival lesions probably explains their tendency to regress during the cold season. Conjunctival vegetations do not do so

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of the classic palpebral form of vernal conjunctivitis is usually not difficult especially when a characteristic history is obtained Sometimes however even in this type some confusion may arise Both the early abortive vernal and the bulbar form are most likely to be misdiagnosed A careful history complete clinical examination including biomicroscopic examination of the cornea and the study of epithelial scrapings of the conjunctiva for eosinophiles are routinely performed

Allergic Conjunctivitis

There should be little difficulty in differentiating acute atopic allergic conjunctivitis from vernal conjunctivitis Similarly allergic dermatoconjunctivitis should rarely if ever present diagnostic problems although the possible association of vernal conjunctivitis with atopic eczema of the eye lids or other causes of eyelid eczema may on rare occasions arise

Chronic microbiallergic conjunctivitis is differentiated from vernal catarrh through the non seasonal character of the symptoms the absence of eosinophiles the clarity of the conjunctival mucosa and the equal distribution of the inflammatory reaction between the upper and lower lids Marked sensitivity to Staphylococcus toxin on skin test also is found in these patients

On the other hand chronic atopic allergic conjunctivitis may at times be easily confused with abortive or early vernal Here the history may not be of particular help as allergies are also likely to occur during the warm season Eosinophiles also occur in the two conditions but are generally found in much larger numbers in vernal conjunctivitis The following points however may be helpful in the differentiation of the two conditions

Appearance of the conjunctiva In chronic atopic conjunctivitis very minute papillae visible only with the slit lamp are seen The conjunctiva moreover is thin and transparent so that the markings are never obliterated There may be only slight hyperemia or even a completely normal appearance In the vernal type on the other hand one generally finds a milky tint due to the opaque quality of the conjunctiva Moreover papillae are larger and may be seen with a loupe Even in the abortive type of vernal the major conjunctival involvement is of the upper lid while in atopic conjunctivitis the reaction involves the entire conjunctiva Moreover no matter how long chronic allergic conjunctivitis continues to recur none of the interstitial changes leading to fibrosis characteristic *of vernal conjunctivitis ever develops*

The secretion In chronic allergic conjunctivitis this may be meager and watery while in vernal it is stringy and sticky Should no membrane be

visible membrane formation may be stimulated in vernal catarrh by *eversion of the upper lid massage of the closed lids* or exposure to intense heat Such a membrane occurs on the upper lid conjunctiva

Response to therapy Chronic allergic conjunctivitis particularly of the atopic variety often responds readily to vasoconstrictors applied topically as well as to the systemic use of antihistaminics Patients with vernal conjunctivitis hardly ever react favorably to antihistaminics and only slightly to the vasoconstrictors

Trachoma

In those countries where both of these diseases are prevalent this differential which should not be a difficult one nevertheless presents itself The two conditions of course may coexist In both vernal conjunctivitis and trachoma the major involvement is of the upper lid conjunctiva However the clinical appearance of the vegetations which are basically papillary in nature despite the large size they may assume the massive conjunctival eosinophilia combined with the usual lack of response to *sulfonamides or the broad spectrum antibiotics should rule out trachoma* Furthermore a trachomatous pannus generally has a considerably different appearance from the usual corneal complications of vernal catarrh being fleshier and more vascularized The pannus of vernal catarrh moreover has a crescentic shape

Additional aids in the differentiation of the two entities are the preauricular lymphadenopathy common in early trachoma and the presence of intracellular epithelial virus inclusion bodies as well as the large numbers of polymorphs and lymphocytes but not eosinophiles found in epithelial scrapings in acute trachoma

Phlyctenular Conjunctivitis

The limbic proliferations of vernal conjunctivitis may at times be confused with phlyctenules The latter however usually stain with fluorescein because they undergo ulceration Furthermore *there is much more* injection and more inflammatory reaction in general in phlyctenular conjunctivitis as well as much more photophobia as compared to itching Lastly there is no conjunctival eosinophilia

Follicular Conjunctivitis

This should usually not present a great problem most cases of follicular conjunctivitis with the exception of trachoma are characterized by primarily *lower lid involvement* as well as considerable preauricular lymphadenopathy While the vegetations of vernal conjunctivitis are often larger in size than follicles careful examination will reveal their papillary

character Moreover epithelial scrapings in vernal conjunctivitis will show eosinophiles while the cellular response in follicular conjunctivitis is often diagnostic in its own right revealing mononuclears or epithelial virus inclusions

ETIOLOGY

The discussion of the pathogenesis of vernal conjunctivitis was deferred until this part of the chapter because the absence of any proven cause made such an approach the most feasible The voluminous literature on the subject that has accumulated throughout the many years the disease has been studied by ophthalmologists throughout the entire world contains many observations as well as speculations of varying interest and value There is neither need nor space to consider all of them here Only those contributions that are felt to be of some importance historic or otherwise will be evaluated by us in the light of our own experiences For more complete coverage of the literature the reader is referred to Beigelman (1)

The Terrain

At the onset we must consider what Lagrange (27) has so aptly called the terrain of vernal conjunctivitis The special predilection of the disease for children especially boys has already been noted This well established fact has stimulated studies of the essential makeup of such individuals It has been thought that vasomotor instability vagotonia and particularly endocrine dyscrasias are etiologically important

Autonomic imbalance According to certain observers (28 29) there would appear to be some degree of vagotonia exhibited by many cases of vernal conjunctivitis This is characterized by excessive excitability of the vagus nerve dermographism and an exaggerated response to the injection of pilocarpine with little or no reaction to the injection of atropine or adrenalin However in itself the evidence would hardly be called convincing Moreover patients with abnormal reactivity of the sympathetic (as distinguished from the parasympathetic) system have also been observed—seven per cent in one series (30)

The Role of Endocrines

Perhaps more provocative and certainly more fundamental is the question of endocrine dysfunction in vernal conjunctivitis Lagrange believed that hypogonadism in boys and ovarian deficiency in women are basic in the genesis of the disease He reported some dramatic cures following the use of indicated gonadal therapy His first observation concerned a woman of thirty who developed vernal conjunctivitis following oophorectomy The eyes responded to ovarian therapy One boy had a

goiter as well as poor testicular development His vernal conjunctivitis cleared when his glands improved In several patients with very small testicles and hay fever the vernal conjunctivitis likewise disappeared after treatment limited to testicular extract only The special tendency of vernal catarrh to disappear after puberty, unlike most allergies made Lagrange feel that the cure is the result of a slow or sudden transformation in the endocrine system at that time It is interesting that despite his orientation and leanings toward allergy, Lagrange believed that vernal catarrh ocurs on the basis of changes in the neuro organo vegetative systems with endocrine dysfunction

Others have come to somewhat similar conclusions Puig Solanes (30) and Fierro del Rio (31) both believe that a gonado hypophyseal disorder existed in these patients Rossi (32) has studied the subject extensively and is convinced that a combined endocrine disorder, involving hypoadrenalism, hypogenitalism and hyperthymism is operative Lippi (33) while postulating an allergic diathesis for the disease, also subscribes to the concept that a basic endocrine disorder of complex nature is present The association of vernal conjunctivitis with large and persistent thymus glands and generalized lymphatic hyperplasia is a point stressed by numerous observers

The value, and perhaps the actual validity, of these observations in the light of the difficulties inherent in all endocrinologic investigation especially the older ones, made when this specialty was in its infancy is of course moot However no one can negate the essential facts that vernal conjunctivitis generally predominates in boys and clears at puberty It would certainly appear worthwhile to study more cases of vernal conjunctivitis from the endocrinologic viewpoint using the more accurate methods now available in order to explain this

Physical Factors

The undoubted relationship of vernal conjunctivitis to warm weather has naturally stimulated investigations concerning the connection of physical and climatic factors like heat humidity and light, with the disease

Heat The importance of temperature itself is obvious There is no question that vernal conjunctivitis is more frequent in warm climates and that even in such regions, as well as in the temperate zones the condition *either becomes aggravated or improves as the temperature rises or fall* There appear to be isolated instances, however, where it or some condition resembling it has occurred in cold climates

Humidity. There appears to be no clear cut evidence indicating that the amount of moisture in the air influences the incidence of vernal conjunctivitis Alimuddin (5) believes that a dry hot climate is worse than

a humid hot environment Others have come to exactly opposite conclusions The relief afforded by air conditioning seems to be due mostly to the lowered temperature rather than the decreased humidity

Light Many observers have attributed the occurrence of the disease to light While light undoubtedly aggravates the symptoms of vernal conjunctivitis photophobia occurs in so many other ocular diseases that this of itself should not be considered of etiologic significance Furthermore it has been pointed out that ultraviolet rays are both stronger and more abundant in precisely those regions where vernal conjunctivitis occurs only rarely and where sufferers often get the greatest relief namely in northern regions such as the Arctic and at high altitudes Moreover it is difficult to see how any form of light especially ultraviolet is capable of causing changes in the palpebral conjunctiva protected as this layer is by the skin and all the intermediary structures of the eyelids As a matter of fact in those experiments where light induced conjunctivitis has occurred it has always been necessary to expose the conjunctiva by eversion of the eyelid Additional evidence against the primary importance of light in vernal conjunctivitis is afforded by the observation of patients who neither improve objectively nor find their clinical course altered significantly despite remaining in darkened surroundings for long periods of time In this connection Axenfeld mentions a case of Fuchs whose patient because of extreme photophobia was forced to remain indoors Yet the disease lasted many years and then like other cases of vernal conjunctivitis cleared up spontaneously

Some basis for suspecting that light might be an etiologic factor in vernal conjunctivitis derives from the well known fact that patients suffering from this disease almost always improve when treated with occlusive bandages only to regress when the dressings are removed An experiment of Bayer (34) would appear to refute this idea In a number of patients with active severe vernal conjunctivitis great improvement was afforded by the use of occlusive bandages in which were incorporated watch glasses rock crystals or thin celluloid all permitting vision as well as the transmission of light rays to the eyes Only when the bandage was airtight however was the treatment successful Upon remission of the symptoms
recurrences soon
important in ve
that all types of glass are capable of filtering out various noxious light rays so that Bayer's observations cannot be accepted as entirely valid

The best known animal experiments concerning the relationship of ultraviolet light to vernal conjunctivitis were reported by Birch Hirschfeld (35) in 1909 He found that in order to evoke any appreciable conjunctival

response in rabbits it was necessary to irradiate the everted eyelids If the stimulus was intense enough, an acute conjunctivitis could be induced which subsided in a few days unless the conjunctiva was exposed to more ultraviolet light This in itself distinguished the reaction from vernal conjunctivitis Repeated treatments resulted in a more chronic inflammatory reaction with eosinophilia Pathologically, this resembled vernal conjunctivitis However clinically, despite the formation of limbal lesions consistent with the disease in humans, the palpebral conjunctiva never developed the characteristic large papillary vegetations, although it did assume the milky appearance with small papillae suggestive of early vernal catarrh Furthermore after a period of intensive treatment a plateau would be reached, beyond which additional exposure gave no increased effect discontinuance of ultraviolet light at this stage resulted in a return to normal in a short period of time, so different from vernal conjunctivitis *On the basis of these observations, Birch Hirschfeld* concluded that ultraviolet radiation was not the cause of vernal conjunctivitis but could aggravate or even result in a recurrence in persons already suffering *from the disease This secondary conclusion was supported much* later by observations of Gallenga (36) Regarding the conjunctival eosinophilia produced by the ultraviolet light, it is our experience that such a *response is readily elicited in rabbits by many irritant chemicals* as well as by physical agents

In the series of cases studied by Maisel, Kornzweig and Lilien (18) general exposure to alpine and infrared light did not cause *any conjunc*tival reaction Cold quartz light (eight exposures to the exposed everted conjunctiva) produced no reaction in any of the patients in whom it was tried

Photosensitivity. That photosensitivity might be a factor in the causation of vernal conjunctivitis is an appealing concept, in view of what is known concerning other forms of physical allergy to light *As Beigelman* and others before him have noted such a special reaction to light might explain away one of the strongest objections to the light theory of vernal conjunctivitis that the lesions occur only in a very negligible *number of* all persons exposed to the same type of light Axenfeld apparently was the first to consider that the conjunctiva might become sensitized to ultraviolet radiation by some substance of endogenous origin Cavara (37) appears to have been the first to consider hematoporphyrin as the substance responsible Impetus to this line of thought was afforded by the apparent photodynamic origin of hydroa estivale which *has been known* to occur in conjunction with limbal lesions similar to those of vernal conjunctivitis In this condition hematoporphyrin is found not infrequently in the urine In vernal catarrh on *the other hand blood* and urine porphyrin studies in general have given negative or inconclusive results

It has been demonstrated experimentally that administration of hematoporphyrin sensitizes animals sufficiently to light so that skin lesions occur However, experiments on the conjunctiva in animals so sensitized did not produce a picture resembling vernal conjunctivitis although they did result in photodynamic inflammation

Beigelman has found that when he gave ultraviolet radiation to the exposed conjunctiva of the everted upper lid of rabbits sensitized by injections of hematoporphyrin proliferative changes occurred in three weeks In nonphotosensitized rabbits two to three months were required to produce similar changes

Pagano (38) reported an interesting case of a sixteen-year old boy with vernal conjunctivitis who developed photophobia and severe itching of the eyes along with a skin reaction after the oral use of sulfonamides He believed that this observation supported the concept that photosensitization of the conjunctiva together with an alteration in porphyrin metabolism plays a role in the etiology of vernal catarrh

Infectious Agents

There is little evidence on the basis of both laboratory and clinical studies that microorganisms play any role in the etiology of vernal catarrh At the present time such a possible causation is generally not even considered However Jurin (39) has recently reported what he considers to be virus inclusions in the epithelial cells in vernal conjunctivitis It should be pointed out that it is very easy to confuse nuclear debris and other findings with inclusion bodies

Allergy

The bases for considering vernal conjunctivitis to be an allergy to a material substance are 1) the periodicity of the disease recurring each year in the warm season 2) the tendency to attack the young especially boys with familial and personal history of allergy 3) the abundance of eosinophiles in the conjunctival secretion 4) the fact that so many patients with vernal conjunctivitis suffer from concurrent atopies such as hay fever asthma atopic dermatitis and allergies to foods dusts and molds 5) the fact that skin and conjunctival tests to pollens, molds and dusts are frequently positive in such patients and 6) the dramatic therapeutic response now obtained by using corticosteroids The self limited character of the disease is often advanced as another argument for its allergic origin Actually children outgrow far fewer allergies than was formerly believed so that this point may no longer be cogent

All these considerations in the light of what we know about allergy in

general would seem superficially to point to an allergic etiology for *vernal conjunctivitis* However despite the apparently strong correlation between the disease and common atopies such as hay fever and despite occasional good reports concerning the value of desensitization to various allergens many observers including ourselves find it difficult to accept the concept that the cause of *vernal conjunctivitis is as simple and clear* cut as all that For one thing on many occasions allergic studies have proved essentially negative Even more important the lack of proof that any one antigen actually causes vernal conjunctivitis coupled with the absence of phenomena such as those of passive transfer would indicate that the case for a typical humoral type of allergy is far from established

While the majority of investigators seem to find as we ourselves have that patients with vernal conjunctivitis have many associated atopies and show numerous positive reactions on both intradermal and conjunctival tests other observers have been unable to demonstrate any significant relationship between material allergens and vernal conjunctivitis Some of these studies were negative in every instance (40 41) as regards to pollen sensitivity A small but exceedingly carefully studied series of eight cases reported by Maisel *Kornzweig* and Lilien (18) revealed 1) that there was no definite familial history of allergy except in one patient 2) that there was no definite association with other allergic phenomena 3) that intradermal testing gave practically negative results and 4) that when dry pollen was instilled in the conjunctival sac in only two patients did mild reactions occur Similar findings have been reported by Lyon (21)

The very multiplicity of allergens found to give positive reactions in patients suffering from vernal conjunctivitis makes one doubt their specificity *in the production of the disease They would appear to include* the entire allergic spectrum of material allergens as well as endogenous hormones Positive reactions to inhalants as one might expect are most commonly encountered Some observers have found intradermal tests to be positive in from fifty to seventy five per cent of all suffering from vernal conjunctivitis In line with these findings Ilelrfeld and Miller (42) have observed that in forty five per cent of their patients conjunctival tests were likewise positive Pollens are the most frequently incriminated allergens but other inhalants found to give positive reactions in vernal conjunctivitis include dust *feathers silk tobacco wool goat epithelium* orris root kapok and pyrethrum Both Gutmann (43) and Feinberg (44) have noted positive skin reactions to molds in their cases of vernal conjunctivitis

Oguchi (45) has reported observations which he feels support his contention (46) that pollens are the etiologic factor in vernal catarrh When pollen was instilled into the conjunctiva of eight patients with pollen hy

persensitivity, but with normal eyes, three developed a condition similar to what these authors considered acute vernal conjunctivitis. In a second group of patients with proven vernal catarrh as well as skin hypersensitivity to pollens, pollen was instilled in the conjunctival sac during the winter, when the ocular condition was quiescent. A flare up in the vernal catarrh occurred in three of the six patients so tested.

On the basis of positive skin tests to foods, food allergies have been hypothecated as a cause of vernal conjunctivitis (42, 47). In this connection some other clinical experiences are of interest. Hansen (48) observed a patient with vernal conjunctivitis who was extremely allergic to chocolate. On eating chocolate during the winter a typical recurrence was noted. Ostrow (49) observed disappearance of the disease when green olives were eliminated from the diet. Ahmuddin (50) found in his large series of patients in Pakistan that sensitivity, particularly to onions and spices but also to beef, eggs, tamarind, brinjal and citrus beverages, did play an etiologic role. Their elimination from the diet was important in the successful treatment of the disease. It should be observed that negative contact reactions to both foods and pollens were noted by Albert and Walzer (51), while pollens, feathers and danders gave positive tests on contact.

The possibility that allergy to intestinal parasites is of some importance in the disease was also advanced by Ahmuddin, inasmuch as in his series of 1050 cases thirty-five per cent were found to have intestinal worms. Of course such a finding is common in Pakistan. However, adequate treatment of these infestations resulted in a cure in a certain percentage of cases. Whether the good results thus obtained might be attributed to the improvement of the general health of the patient or whether there is a specific relationship would be difficult to prove. The role of bacterial allergy has been championed by Cooke (52). He observed that a distinct conjunctival reaction occurred several times following subcutaneous injection of an autogenous vaccine in patients with vernal conjunctivitis.

Autogenous allergy to hormones in combination with a climatic factor as a cause of vernal conjunctivitis has been advanced by Paggy (53). According to him, each factor alone is insufficient to cause the condition. His treatment with astrophore (hormones) was very successful in a number of cases. Working with Zondek, he was able to demonstrate what he thought was autoallergy to endogenous hormones.

Much stress has been placed on those instances where desensitization with pollen extracts has resulted in the cure of what was presumed to be vernal conjunctivitis. This has led many to maintain that the disease is essentially a manifestation of pollen allergy. Unfortunately, such reports, which have been few indeed, are in the main quite incomplete. To our mind, the basis for establishing the diagnosis of vernal conjunctivitis in

these cases was by no means definite Furthermore for good results to occur treatment for from two to three years seems to be necessary in most instances This often brings the patient to the age and stage when vernal conjunctivitis either disappears or improves spontaneously

There is however one case on record (54) in which the objections just mentioned do not obtain The patient was a twenty three year old cattle man who had had symptoms characteristic of the palpebral form of vernal conjunctivitis including a typical cobble stone hyperplasia and conjunctival eosinophilia for less than one year Tests indicated a marked sensitivity to cow s epithelium One drop of a diluted solution caused a severe reaction in the conjunctiva Biopsy of the conjunctiva showed the typical histologic picture of vernal conjunctivitis Desensitization by mean of injections of an extract of cow s epithelium resulted in a cure of the conjunctivitis If this patient had vernal conjunctivitis—as we must on the evidence presented assume he did—this case is of great etiologic interest

On the basis of what we have learned concerning allergy in relation to the etiology of vernal conjunctivitis it appears to us that at the present time we are justified only in concluding that most patients with vernal conjunctivitis manifest associated atopies which appear to play an important role in the terrain or the background of the disease although of themselves these allergies are not the direct cause of the condition As will be hypothecated shortly such allergy may be of considerable significance —even if it is not the sole or precipitating factor etiologically However the very multiplicity of the allergens associated with the condition would indicate that none is specific Even in those cases where desensitization appears to be beneficial it merely proves what we already know that the patient may be allergic and has multiple allergies Positive skin or positive conjunctival tests of themselves do not prove that a particular allergen is the cause of a disease One can etiologically incriminate an antigen causing positive reactions only if its removal makes the symptoms disappear and its use at a later date results in a recurrence It might also be observed that in countries like the United States where hay fever affects as much as three to five per cent of the entire population vernal conjunctivitis is a rare disease with an incidence of less than one tenth of one per cent Moreover in certain localities such as South Florida Arizona and Southern California where presumably due to the high temperature vernal conjunctivitis occurs more frequently than elsewhere the pollen count for ragweed is very low Moreover patients with vernal catarrh suffer from the disease through the entire warm season whereas specific types of hay fever such as the autumnal ragweed variety affect patients only during certain periods of the summer

A Useful Concept of the Etiology

It seems evident that the actual cause of vernal conjunctivitis is not known. Although present day thought leans strongly toward an allergic etiology, both the nature of the excitant and the mechanism involved are still matters of speculation. Our own feeling is that vernal conjunctivitis is a form of physical allergy to the warm season occurring in predisposed atopic individuals. The special factors that predispose these persons may be endocrine, metabolic, allergic and possibly infectious. In an unexplained way the warm season triggers some sort of chain reaction in these patients bringing on the disease. Should one of these factors be eliminated the disease sometimes disappears before it completes its usual prolonged cyclic course. Such a concept, indefinite as it must necessarily be, helps to explain the bizarre picture that the disease presents and offers a common ground for the otherwise apparently contradictory findings of so many excellent observers.

The existence of certain types of allergic reactions of a less clear cut type requiring multiple factors for their flowering is accepted. Although no immunologic mechanism can be demonstrated, such reactions seem best considered in the allergic category. For example, in physical allergy, especially to light, it is known that a number of predisposing factors may be involved. As noted by Harkavy (55), three types of factors may operate: 1) infectious, metabolic, or endocrine; 2) photodynamic, including endogenous porphyrins and exogenous drug administration; and 3) allergic mechanisms. Many other types of allergy have been aggravated or precipitated by simple physical factors such as cold or chilling, or by other unrelated allergens. Although gout has been considered to be a metabolic disturbance, we now think that—at least in some individuals—there is an allergic facet to the disease. A variety of noxious stimuli may trigger the mechanism for acute attacks. These have been precipitated by injections of pollens in gout patients who have hay fever and are also known to occur after chilling and related physical exposures. Of theoretical interest in relating such reactions to the etiology of vernal conjunctivitis are some observations noted by Selye (57) in studying his "general adaptation syndrome," in which the organism reacts to noxious stimuli by responses initiated by the pituitary-adrenal mechanism. He points out that: 1) heat stroke and solar radiation in shaved guinea pigs will give the alarm reaction, 2) intense ultraviolet light will give the blood changes typical of shock, 3) individuals pretreated with photodynamic substances exhibit especially marked alarm reactions when exposed to light, and 4) climatic conditions in weather sensitive individuals cause the alarm reaction.

It is thus possible that the factors mentioned in this section—glandular

metabolic autonomic, and allergic—all combine in some manner to condition the atopic individual, so that some ingredient of the warm environment, probably heat itself rather than light, causes the physical allergy we know as vernal conjunctivitis Any one of these predisposing factors may trigger the chain reaction bringing on the condition or, on the other hand, the elimination of any one factor may possibly block the reaction resulting in cure or amelioration of the disease

TREATMENT

As might be inferred from what we have written so far, the treatment of vernal conjunctivitis, except in the rarest of instances, is at best palliative In the absence of a known cause, on general principles any claims of cure must be considered very cautiously As just mentioned, even in those instances where the elimination of certain foods or desensitization is stated to have been successful, it is best to assume that somehow the chain reaction or set of circumstances bringing on the disease has been interrupted Our newer knowledge of the blocking action and value of the corticosteroids in vernal conjunctivitis has not only highlighted therapy along these lines, but may also serve to explain occasional good results from the use of other agents and methods having no apparent therapeutic rationale The basis for improvement in such cases may be nonspecific by inducing increased activity of the adrenal cortex

Change of Climate

Since warm weather plays such an important role in the causation and exacerbation of vernal conjunctivitis, even in the rare perennial cases the most obvious treatment would appear to be climatic Removal to a cooler climate such as Maine, Canada, or Alaska, is helpful While a certain amount of relief often occurs particularly severe cases may not respond as satisfactorily This is probably because so few places that are reasonably available to patients become cold enough to cause a complete cessation of symptoms If the sufferer from vernal conjunctivitis should for example leave the northern hemisphere in the summer for the winter of the southern hemisphere that is an entirely different matter Generally speaking however, change of climate is usually not feasible, and only partially effective

In line with this air conditioning appears to be of some value, more for its cooling effect than for the elimination of any possible air-borne excitants Its value is, however, limited by the fact that patients cannot always stay indoors

Steroid Therapy

The introduction of the corticosteroids has resulted in a tremendous advance in the management of vernal conjunctivitis The use of these

agents either topically or systemically in dosages adequately tailored to the individual case causes marked and immediate improvement symptomatic at first objective later This nonspecific blocking action is only temporary however and ceases when their administration is stopped

The local use of ophthalmic solutions of hydrocortisone (0 5 to 2 5 per cent) or cortisone four to six times daily often is sufficient to afford great relief in mild instances of vernal conjunctivitis especially of the limbal variety The symptoms are greatly alleviated the discharge diminishes conjunctival eosinophilia becomes less marked and the limbic proliferations may disappear entirely The local application of prednisone prednisolone and other synthetic products of this group are equally of value

In the palpebral variety while equally dramatic results may at times be obtained particularly at periods during the year when symptoms are not at their height the results from local therapy alone are generally not as good After an initial trial of topical treatment these patients should be started on fairly large systemic doses of cortisone hydrocortisone prednisone or prednisolone As soon as improvement becomes manifest these large doses may be gradually reduced to maintenance ones that vary with each individual but may be as low as twelve and one half milligrams of cortisone once or twice a week or correspondingly small amounts of the newer steroids In such cases strangely enough the local use of steroids now becomes effective even if previously of little value

In rare instances however nothing appears to suffice except the use initially of corticotropin starting with dosages of approximately forty units a day Once a definite improvement occurs this dose may be lowered rapidly and other steroids used systemically

Fortunately even in such patients once the condition is under control much smaller doses suffice for maintenance therapy The usual precautions must be observed however since the patients are younger and less prone to suffer from the sequelae of water retention or other metabolic disturbances prolonged treatment is generally quite safe

To repeat where steroid therapy is successful the almost immediate symptomatic improvement that occurs with disappearance of itching photophobia and tearing is accompanied by marked diminution both in the discharge and in membrane formation Resolution of the relatively small limbal excrescences soon follows Palpebral vegetations also shrink perceptibly but only the smaller and fresher of these entirely resolve In fact the marked palpebral proliferations characteristic of severe long standing vernal conjunctivitis disappear completely only in rare instances

Steroids are especially effective in the corneal complication of the disease Here dramatic improvement with clearing usually occurs in a short

time Salvi (58) feels that results with cortisone are superior to those with the use of corticotropin

Other Medicaments and Medications of Value

Many patients suffering from vernal conjunctivitis obtain considerable relief from those measures directed towards the removal of the thick secretion characteristic of the disease That is why these patients rub their eyes so much Besides relieving the itching rubbing aids in the formation of a membrane which then exudes A one or two per cent solution of monohydrated sodium carbonate (three drops four times a day) has been advocated Other alkaline solutions such as sodium carbonate buffered to a pH of 8 4 or three per cent solution of sodium bicarbonate have been used The rationale for such alkaline solutions appears to be that mucin which is present in high content in the discharge of vernal catarrh either dissolves or disintegrates more readily at high pH Streptodornase and streptokinase may also prove valuable for this purpose

Conversely boric acid or weak solutions of acetic acid have also been used on the basis of counteracting the high alkalinity of the secretion On the same premise sodium propionate which breaks down to form propionic acid particularly in solutions buffered to a pH of 6 0 has been helpful in many patients with vernal conjunctivitis

Vasoconstrictors such as epinephrine (0 01 per cent) privine (0 05 per cent) neosynephrine (0 12 per cent) and tyzine (0 05 per cent) are likewise all valuable Subconjunctival injections of adrenalin are said to be beneficial especially in limbal vernal Local anesthetics especially those that are less prone to result in allergic dermatoconjunctivitis such as holocaine (0 2 per cent) or cocaine (0 3 per cent) are often of great help in relieving the itching

When both vasoconstrictors and anesthetics are combined with weak (2 5 per cent) solutions of sodium propionate their efficacy appears increased

Miscellaneous Drugs and Measures

Many other drugs and procedures have been advocated as having merit in the treatment of vernal conjunctivitis A few of these are noted here

Antihistaminics We have found the use of antihistaminics either locally or systemically entirely ineffective in proved vernal conjunctivitis We are aware of reports which are at variance with this conclusion Since systemic antihistaminics are of value in those types of atopic conjunctivitis most readily confused with vernal catarrh accurate diagnosis is very important Furthermore it must be remembered that some antihistaminics have local anesthetic properties

Calcium Intravenous injection of calcium a very popular form of therapy for many unrelated conditions has been tried extensively in vernal conjunctivitis There seems to be little evidence to justify this form of treatment although in Egypt Lyons (21) has found it generally beneficial in young patients or in patients with symptoms during the winter These two groups had low blood calcium measurements according to him

Other forms of endocrine therapy. The reports of LaGrange Paggy and others concerning the use of gonadal or other hormonal extracts have already been noted In the light of what we now know concerning the corticosteroids it is possible that some of the beneficial results reported *following the administration of endocrine products may have been due* at least in part to influences on the adrenals

Tissue therapy Kriz (60) claims to have obtained favorable results in many ophthalmic conditions including vernal conjunctivitis by means of tissue therapy with preserved placental extract prepared according to the method of Filatov

Vitamin therapy Certain authors among them Stern (61) and Gutmann (62) have maintained that the use of riboflavin is beneficial in vernal conjunctivitis Stern has attributed this at least in part to the antihistaminic properties of riboflavin He has advocated the oral administration of ten milligrams daily Gutmann prefers intramuscular injections Kadlecová (63) successfully used riboflavin in a case of atypical vernal conjunctivitis of the bulbar variety where ariboflavinosis was present attributing its action to both its antihistaminic and its reducing actions

Intramuscular injections of cod liver oil are advocated by Sakic (6) and Skolouk (64) The latter followed the method of Filatov

Physical Therapy

Iced compresses often give great relief when used three to five times a day

Occlusive bandages as noted above may result in dramatic improvement in vernal conjunctivitis especially in the limbal variety Since this improvement when it does occur is maintained only when the eye is covered it would appear to have little current value except where corneal complications require a dressing for other reasons However it might be worthwhile to resort to this method for the first day or two in severe cases until the effect of systemic corticosteroids used concomitantly has begun The bandage often included an airtight watchglass It may be recalled that the value of the method apparently was due not to the elimination of light but to its airtight character

There is little definite information available as to any specific value of dark glasses in vernal conjunctivitis In an earlier era however they were

used by many ophthalmologists, especially in the form of tightly fitting protective spectacles According to Gallenga (36), patients with vernal catarrh are most comfortable when using glasses permitting passage of light only in wave lengths above 6000 A U The use of glasses allowing exposure to light of intermediate wave lengths (5100 A U) had no influence on either the objective or the subjective symptoms However a definite intolerance with worsening of the condition occurred with light below 4600 A U Alvarado (65) believes that all types of tinted glasses especially amber are useful because of the elimination of ultraviolet rays He considers that vernal conjunctivitis results from such radiation in vitamin deficient individuals

Radiotherapy

Before the advent of steroid therapy, radiotherapy in all its forms including x ray radium and beta radiation held a very important place in the treatment of severe vernal conjunctivitis Introduced over fifty year ago the use of these modalities had been found at times to be very efficacious, providing great improvement or even permanent cure in many patients However, the attendant complications (among them cataracts corneal erosions and ulcers and dystrophic changes of the conjunctiva resulting in loss of smoothness roughening and secondary corneal irritation) have always made this form of treatment hazardous The introduction of a satisfactory beta radium applicator offered a much safer superficial form of such treatment Since beta radiation penetrates only two millimeters the lens appears to be protected from damage The best results occur when treatment is done early in the disease At this stage the papillae are more sensitive to the obliterative endarteritis produced by radiotherapy In cases of longer duration the large amount of hyalinization which is present causes radioresistance For this reason the surgical removal of vegetations has been advised in long standing cases before radiotherapy is started From the reports of Iliff (66) Okrainetz (67) Hughes (68) and Moore (69) the results appear to be at least as good with beta radiation as with other forms of radiation while the complications that occur are both less frequent and less severe Advocates of the method maintain that permanent cure often occurs although some cases apparently need a small amount of additional treatment the following season

Moore advises the use of beta radiation in those sufferers from vernal conjunctivitis with marked lesions who are made only slightly more comfortable by the use of topical cortisone He feels that in this group beta radiation offers a cure in most cases attended by little or no risk His procedure, using radon or strontium 90 is to start with an initial dose of

3000 millicurie-seconds This is followed by three more treatments (5000 millicurie-seconds) at weekly intervals This course is followed by a rest period of from two to three weeks at which time another course of treatment is undertaken Of six patients with palpebral lesions, in whom treatment consisted of 17,000 to 45 000 millicurie-seconds over periods of from two to four months, cobblestone lesions disappeared in three One patient obtained symptomatic relief when topical cortisone was then given The remaining two patients obtained symptomatic relief but resolution of the lesions was incomplete despite dosages up to 88,000 millicurie seconds In seven patients with limbal lesions five who were followed for twelve months obtained what he called wonderful results after treatment with from 25 000 to 53 000 millicurie seconds

Our own experience since the advent of corticosteroids has been that the intensive use of these hormones both systemically and topically has made the use of radiotherapy in any form unnecessary Moreover, prior to their introduction it was our own feeling that from the long-term point of view radiotherapy was dangerous (even though beta radiation apparently was less so) and was justified only in rare instances It was felt that in a self-limited disease if one could tide the patient over his worst periods it was far safer to avoid especially in such young patients possible permanent damage to the delicate ocular tissues which may become apparent only many years later Moreover it is difficult to prognosticate in any given case whether or not radiotherapy would be effective Needless to say treatment should be given only by experts in this field

Harte and Dimitriou (70) believed that they obtained beneficial results in vernal conjunctivitis after repeated weekly applications of x-ray to the spleen The improvement was most marked as regards the limbal manifestations which generally disappeared the palpebral vegetations while diminishing in size did not go away

Surgical Therapy

The simplest form of surgical therapy and generally the most effective is the removal of large palpebral vegetations This is especially indicated when the corneal complications are severe Moreover the removal of such proliferations facilitates the elimination of the discharge which is generally quite adherent between the vegetations As noted above, the removal of vegetations is advocated prior to radiotherapy This procedure is often easily done with scissors However the use of cauterizing agents such as trichloracetic acid as well as freezing with carbon dioxide snow has been advocated The latter in addition to destroying vegetations appears to exert beneficial effects by inducing a secondary cellular and humoral reaction Ethyl chloride has also been used for this purpose

There appears to be no justification for tarsectomy as vernal conjunctivitis does not involve the tarsus Operations on the palpebral conjunctiva would appear to have more of a rationale Goldstein (71) advocated mucous membrane grafts obtained from the buccal mucosa after extensive removal of the involved conjunctiva He claimed good results but we ourselves having assisted at some of these operations had the opportunity to observe such patients postoperatively and were not impressed with the long-term benefits of this operation Paufique (72) has recently returned to this procedure advocating it for refractory cases not responding to corticotropin steroids or beta radiation

Shimkin (73) performs surgical removal of the entire tarsal conjunctiva and replaces it by the mobilized conjunctiva of the fornix

Specific Allergic Desensitization

As noted above sporadic cases have been reported in which cure of vernal conjunctivitis apparently occurred following such desensitization We feel that in the rare instance in which such a cure actually occurred the chain reaction responsible for the vernal conjunctivitis had in some way been interrupted It appears to us that most of the reported cures may not have been in cases of vernal conjunctivitis at all or else improvement may have resulted from both simultaneous local treatment and the natural progress of the disease towards healing The special instance reported by Eriksen mentioned earlier in this chapter where pathologically proved vernal conjunctivitis was related to allergy to cow s epithelium and successfully treated by specific desensitization should be noted It is interesting however that Eriksen himself calls his case an allergic conditioned case of conjunctivitis vernalis by implication apparently indicating a concept that has been maintained by us—that a chain of events or circumstances had been interrupted thus stopping the disease process In general a good rule to follow is if the associated atopies occurring in a patient with vernal conjunctivitis are severe enough in their own right to require desensitization therapy this form of treatment should by all means be undertaken Where this is successful even if only partially the treatment is certainly justified and added dividends may possibly further accrue through indirect amelioration of the vernal conjunctivitis by means of the mechanisms we have suggested throughout this chapter

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There appears to be no justification for tarsectomy as vernal conjunctivitis does not involve the tarsus Operations on the palpebral conjunctiva would appear to have more of a rationale Goldstein (71) advocated mucous membrane grafts obtained from the buccal mucosa after extensive removal of the involved conjunctiva He claimed good results but we ourselves having assisted at some of these operations had the opportunity to observe such patients postoperatively and were not impressed with the long term benefits of this operation Paufique (72) has recently returned to this procedure advocating it for refractory cases not responding to corticotropin steroids or beta radiation

Shimkin (73) performs surgical removal of the entire tarsal conjunctiva and replaces it by the mobilized conjunctiva of the fornix

Specific Allergic Desensitization

As noted above sporadic cases have been reported in which cure of vernal conjunctivitis apparently occurred following such desensitization We feel that in the rare instance in which such a cure actually occurred the chain reaction responsible for the vernal conjunctivitis had in some way been interrupted It appears to us that most of the reported cures may not have been in cases of vernal conjunctivitis at all or else improvement may have resulted from both simultaneous local treatment and the natural progress of the disease towards healing The special instance reported by Eriksen mentioned earlier in this chapter where pathologically proved vernal conjunctivitis was related to allergy to cow s epithelium and successfully treated by specific desensitization should be noted It i interesting however that Eriksen himself calls his case an allergic conditioned case of conjunctivitis vernalis by implication apparently indicating a concept that has been maintained by us—that a chain of events or circumstances had been interrupted thus stopping the disease process In general a good rule to follow i if the associated atopics occurring in a patient with vernal conjunctivitis are severe enough in their own right to require desensitization therapy this form of treatment should by all means be undertaken Where this is successful even if only partially the treatment is certainly justified and added dividends may possibly further accrue through indirect amelioration of the vernal conjunctivitis by mean of the mechanisms we have suggested throughout this chapter

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9

DIAGNOSTIC AIDS IN CONJUNCTIVITIS

Since conjunctival allergies are often confused with other forms of conjunctivitis, sometimes with unfortunate results, an outline of laboratory and clinical aids in the differential diagnosis of conjunctivitis and a discussion of the oculo-muco-cutaneous syndromes are presented in this chapter

LABORATORY AIDS

In general, the laboratory procedures of most value in the differential diagnosis of the external allergies of the eyes from other forms of external inflammation are simple enough to perform in routine office practice The ophthalmologist who utilizes them in a practical manner, in conjunction with careful clinical observation, will find the management of his patients with such clinical complaints a great deal easier and much more efficient This section will deal only with 1) bacterial cultures, 2) secretion smears of the conjunctiva and 3) epithelial scrapings of the conjunctiva and lid margins Other tests useful in the diagnosis of allergies of the eyes such as skin tests (both intradermal and patch) and conjunctival tests are covered in other parts of the text In some instances of resistant conjunctivitis biopsy, often overlooked, may reveal entirely unsuspected neoplastic disease

Indications for Laboratory Tests

The first aim of the laboratory in the practical management of external ocular diseases is to aid in making the necessary broad group differential diagnosis that is the keystone of successful treatment Once this is estab

lished the usual prompt response to indicated therapy often makes it unnecessary, in the average case to proceed to a more specific laboratory diagnosis Thus in the evaluation of a case of conjunctivitis it is important to differentiate bacterial conjunctivitis as a general entity without necessarily determining the bacteria present from viral types of conjunctivitis as the prognosis and treatment are quite different in those two groups Similarly allergic conjunctivitis must be recognized even though the specific allergen is not found Epithelial scrapings (1) because they reveal the character of the conjunctival response afford an excellent and rapid means of making this basic group differential Moreover only by this method is information obtained concerning the conjunctival epithelial cells virus inclusion bodies and the earliest evidence of specific bacterial or fungal infection all very important in the evaluation of conjunctivitis For these reasons epithelial scrapings of the conjunctiva should always be examined in conjunctivitis not only because of their basic differential value but because in many instances a specific definitive diagnosis is readily made without recourse to further laboratory studies

In acute bacterial conjunctivitis secretion smears afford an additional source of rapid useful information In acute infections of the conjunctiva cultures are not indicated unless infection is unusual in character or of great severity Slide examination generally affords a much more rapid and sufficiently reliable method of diagnosis Moreover since some ocular pathogens are not too easily cultivated cultures may show no growth at all in cases where numerous organisms are to be found on smears and scrapings On the other hand cultures of the conjunctiva and lid margins are always indicated in chronic inflammations of the eyes and should be routinely employed along with scrapings in the evaluation of resistant chronic cases In these patients the additional expense entailed is more than compensated by the resultant advantages In acute central corneal ulcers cultures should always be performed Facilities for the cultivation of viruses are not universally available

Cultures of the Conjunctiva and Lid Margins

Usually the only organism if any found on culture of the healthy conjunctiva and lid margins are nonpathogenic white staphylococci and diphtheroid bacilli Occasionally however one or two colonies of bacteria generally considered pathogenic such as *Staphylococcus aureus* Streptococcus and pneumococcus are encountered For this reason to be of any practical value conjunctival cultures must be obtained in a manner that insures an accurate quantitative estimation of the number of colonies of each type of bacteria present in each site cultured This requires plating

on solid media Using cotton applicators moistened with glucose broth cultures of the conjunctiva and lid margins of each eye (four sites) are plated immediately on blood agar The lid margins and the meibomian glands must always be cultured because they often are the source of the presenting conjunctivitis and ocular eczema Even if only one eye is involved both should be cultured for quantitative comparison often diagnostically valuable Occasional rare colonies of ocular pathogens mean nothing numerous colonies are of great significance Furthermore because non toxin producing staphylococci are clinically of no importance while toxin producing staphylococci play an exceedingly important role in the causation of external ocular infections especially chronic blepharoconjunctivitis no laboratory report is significant unless determination of the probable pathogenicity of the staphylococci present is included Accepted laboratory indications of toxin production of staphylococci include 1) pigment formation (aureus), 2) hemolysis 3) mannitol fermentation and 4) coagulation of blood plasma (coagulase test) These tests are very easily performed and are an integral part of the examination Unfortunately *unless the clinician explains the importance of these really simple* but fundamental requirements and insists that they be adhered to few general laboratories will take and report eye cultures in a satisfactory manner Left to their own practices they will merely identify the organism *Such an incomplete report is of no practical diagnostic value*

Special media like Loeffler s for suspected diphtheria chocolate agar for Neisseria or Sabouraud s for fungi are used when clinically indicated

Secretion Smears

Smears of conjunctival secretion are obtained by either a cotton applicator or a platinum loop On rare occasions special stains are required but usually the Gram stain or even a simple one like methylene blue is satisfactory Once the ophthalmologist becomes acquainted with the appearance on conjunctival smear of the relatively few organisms causing most conjunctivitis he is generally able to recognize the causative organism on the basis of morphology and staining characteristics alone (2) (table 4) Difficulties are sometimes encountered in differentiating Gram negative bacilli especially pyocyaneus unless the source such as a *fulminating* corneal ulcer strongly suggests its nature It is impossible to differentiate the gonococcus from the meningococcus on smear alone as this requires cultural methods In the United States at the present time in the absence *of active venereal infection purulent conjunctivitis* due to a Gram negative diplococcus is much more apt to be meningococcal than gonococcal except in the newborn (2a) Therefore even the suggestion of a gonococcal etiology may result in irreparable injustice to the patient

TABLE 4

The appearance of common bacteria and fungi in conjunctival exudates and epithelial scrapings (1 ?)

1 *Cocci*

a Gram positive

1 Round occurring usually singly or in pairs rarely clusters often few in numbers, never on living epithelial cells *Micrococcus pyogenes* var *aureus* (Staphylococcus)

2 Round occurring in pairs or short chains usually not on living epithelial cells Streptococcus

3 Lancet-shaped diplococci (end to end) epithelial parasite *D pneumoniae*

4 Varying-sized, often minute coccoid bodies (frequently intra-cellular) Streptothrix

5 Large round varying-sized budding yeast *Pityrosporum ovale*

b Gram negative

1 Numerous coffee-bean-shaped (side to side) intra-cellular diplococci found on living epithelial cells much pus *N gonorrhoea* (gonococcus) or *N meningitidis* (meningococcus)

2 Similar morphology not intra-cellular nor epithelial parasite little pus *N catarrhalis*

2 *Bacilli*

a Gram-positive

1 Pleomorphic large, curved club-shaped epithelial parasite *C diphtheriae*

2 Similar morphology not epithelial parasite *C xerosis*

3 Short fat clubbed not epithelial parasite *C hofmanni*

4 Branching forms and filaments Streptothrix

b Gram negative

1 Large diplobacillus (end to end) numerous no pus epithelial parasite *Morazella lacunata (B morax-axenfeld)*

2 Always single encapsulated *Klebsiella pneumoniae (B friedlander)*

3 Large rod *E coli*

4 Minute cocco bacillus not epithelial parasite *H influenzae*

5 Minute slender rod epithelial parasite *H conjunctivitidis (B koch-weeks)*

6 Minute slender rod *Ps aeruginosa (B pyocyaneus)*

Scrapings of the Conjunctival Epithelium and Lid Margins

Material is obtained from the cocainized conjunctival site of maximal involvement by means of a platinum spatula (fig 43) and spread evenly and thinly upon a glass slide previously cleaned with alcohol Specimens of the lid margin are similarly obtained After fixation in methyl alcohol for five minutes the slide is immersed in a Coplin jar containing dilute Giemsa solution (one drop of concentrated Giemsa stain to every two cubic centimeters of neutral distilled water) and allowed to stain overnight It is then passed through ninety-five per cent ethyl alcohol very rapidly allowed to dry and then examined For more rapid examination immersion



FIG 43 Technique of obtaining epithelial scrapings of palpebral conjunctiva with platinum spatula The same spatula may be used for scrapings of the lid margin bulbar conjunctiva and cornea (Theodore (4))

in a solution containing one drop of Giemsa per cubic centimeter of water for one hour will suffice It is important that the distilled water used is neutral If the water is acid a ruined slide with an eosinophilic stain results if it is alkaline an equally useless diffuse basophilic stain occurs Wright s stain is also used for epithelial scrapings but it is not as satisfactory as Giemsa

The normal conjunctiva Scrapings of the normal conjunctiva reveal epithelial cells having large round vesiculated purplish nuclei usually situated in a slightly granular light blue cytoplasm In the colored races particles of green black melanin pigment occur normally in the cytoplasm of the cells particularly in the bulbar conjunctiva One must not mistake this pigment for virus inclusion bodies which have a blue red color Leukocytes are not present in significant numbers in the normal conjunctiva neither are macrophages Fibrin recognized by a diffuse red color and mucus which occurs in ribbon like shred are also not found in scrapings in the normal conjunctiva

Conjunctival Exudates

When leukocytes of any type occur in more than occasional frequency conjunctival inflammation is present The diagnostic significance of the various responses is noted below (1) (3)

Polymorphonuclear (neutrophilic) response. An essentially mucopurulent or purulent exudate occurs in

1. Infection due to all bacteria, except *M. catarrhalis* and *M. lacunata* (Morax-Axenfeld) where much fibrin and no mucus is found
2. Acute allergies, where often considerable purulent discharge occurs
3. Fungi, especially in Streptothrix canaliculitis
4. Infection due to 'intermediate' viruses (chlamydozoaceae) (a) trachoma, (b) inclusion conjunctivitis, (c) lymphogranuloma venereum
5. Erythema multiforme and its possible variants
6. Reiter's syndrome
7. Early ocular pemphigus

Mononuclear response. Mononuclear exudates (usually small lymphocytes) occur in the following virus infections causing follicular conjunctivitis

1. Epidemic keratoconjunctivitis (at the onset there may be an increased number of polymorphs)
2. Acute follicular conjunctivitis of Beal
3. Adenoido-pharyngo-conjunctival fever
4. Herpes simplex conjunctivitis
5. Newcastle disease conjunctivitis
6. Conjunctivitis secondary to eyelid infection by either molluscum contagiosum or verruca vulgaris

Mononuclears are also found in chronic irritations of the conjunctiva due to drugs, especially the miotic alkaloids, or to industrial irritants.

Eosinophilic or basophilic response. Conjunctival eosinophilia is almost pathognomonic of vernal conjunctivitis or allergic conjunctivitis, assuming that one can rule out other conditions in which eosinophils occur. A positive finding is diagnostically valuable, but the failure to find any eosinophils does not rule out allergy (4). Increased blood eosinophilia, such as in parasitic diseases, does not result in conjunctival eosinophilia unless bleeding occurs while performing a scraping. Often the outstanding feature is the presence of huge numbers of eosinophilic granules due to the fragmentation of the eosinophils. Such fragmentation, which is especially common in vernal conjunctivitis, may distinguish this condition from atopic allergic conjunctivitis, where such fragmentation is less frequent unless the inflammation is especially severe. Day to day variation in the number of eosinophils encountered is common and must not be considered in itself indicative of either improvement or exacerbation of the allergy. Sometimes, especially in vernal catarrh or in drug allergies, only basophils are found.

addition to much mucus and an increased number of goblet cells Diphtheroid bacilli are not found proliferating on the epithelial cells

4 *Cicatrization* of the conjunctiva as in old trachoma ocular pemphigus or radiotherapy

5 *Exposure* of the conjunctiva as in ectropion

At the lid margin keratinization occurs normally, to avoid error the exact source of all scrapings must be noted

Epithelial virus inclusions 1 *The chlamydozoaceae* These include trachoma inclusion conjunctivitis, and lymphogranuloma venereum

Epithelial scrapings of the conjunctiva afford the only laboratory means of demonstrating the cytoplasmic virus inclusions causing these infections and are an important diagnostic aid The virus elementary body (0 25 micron), staining blue-red with Giemsa penetrates the epithelial cell cytoplasm forming what is known as an inclusion body Going through a cycle, the elementary body first enlarges and divides forming larger initial bodies (0 75 micron) which stain blue Later, however when the growing inclusion body fills most of the epithelial cell, the virus reverts to its original form so that when the swollen cell membrane finally ruptures fresh elementary bodies are released for the invasion of other cells The three viruses cannot be differentiated on morphology, but since their clinical manifestations are so different the finding of cytoplasmic inclusion bodies affords positive diagnosis in each instance

In searching for virus inclusion bodies the examiner rapidly scans the slide under low power looking for any gross evidence of cytoplasmic inclusions in the epithelial cells The oil immersion lens is then employed for detailed study of suspicious cells Fragmented nuclear and cytoplasmic debris, precipitated stain or melanin pigment must be differentiated In acute stages many inclusion bodies are found later they become much fewer but even the demonstration of one inclusion suffices for diagnosis The use of cortisone locally for several days prior to examination increases the number of inclusions

2 *Inclusion bodies of lesser diagnostic importance* In a number of other human ocular viral infections virus inclusion bodies are generally demonstrable on epithelial scrapings only if special staining techniques are employed Fortunately clinical examination is generally enough for diagnosis so that there is usually no necessity for slide diagnosis These infections include herpes simplex (intranuclear inclusion body) herpes zoster (intranuclear) molluscum contagiosum (cytoplasmic shown best on biopsy) and vaccinia (cytoplasmic)

Inclusion bodies taking the Giemsa stain have been reported in a number of viral and rickettsial ocular infections occurring in animals In human

Major causes of conjunctival eosinophilia or basophilia

1 Vernal conjunctivitis (during recessions eosinophilia may diminish while basophiles increase in number)
2 All types of acute and chronic allergic conjunctivitis (except bacterial allergy) (a) atopic—pollens inhalants danders and (b) contact—drugs cosmetics chemicals apparel
3 Severe chemical or vegetable irritants (lye lime ipecac insect powder indelible pencil ricin turpentine) result in massive eosinophilia This is encountered in industry or as a self induced conjunctivitis (malingering)
4 Conjunctival parasites myiasis insects hornet stings sporotrichosis and trypanosomiasis
5 Ocular pemphigus (later stages)

While conjunctival eosinophilia is an important manifestation in drug allergy it does not occur in drug intolerance due to drug irritation such as is encountered with the miotic alkaloids and the synthetic miotics Neither does it occur in phlyctenular keratoconjunctivitis a valuable point in the differentiation of this condition from the limbic form of vernal conjunctivitis Eosinophilia has been encountered on rare occasions in staphylococcal and viral conjunctivitis These infections may have been complicated by underlying allergy

Macrophages and plasma cells Giant cell macrophages (Leber cells) and lymphoblasts are found on expression of trachomatous follicles Macrophages also occur in the conjunctival exudate of inclusion conjunctivitis Plasma cells occur in the exudates of trachoma

The abnormal conjunctival epithelium Degeneration of the conjunctival epithelial cells with keratinization characterized by a smooth reddish cytoplasm and nuclear degeneration (pyknosis karyorrhexis karyolysis) occurs as a result of dryness of the conjunctiva especially in

1 *Deficiency of vitamin A (xerophthalmia)* Here scrapings of the bulbar conjunctiva especially of a Bitot s spot classically reveal keratinized epithelial cells upon which myriads of xerosis bacilli (diphtheroids) proliferate In prexerosis early keratinization may be accompanied by increased melanin pigmentation of the cytoplasm

2 *Epithelial plaques* These lesions have a similar appearance to a Bitot s spot both clinically and on epithelial scrapings (5) Differentiation between the two entities lies in the absence of other signs of avitaminosis A and lack of response to vitamin A therapy when a plaque occurs

3 *Keratoconjunctivitis sicca* In this condition scrapings are diagnostically valuable because keratinization of considerable degree is found in

addition to much mucus and an increased number of goblet cells Diphtheroid bacilli are not found proliferating on the epithelial cells

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Inclusion bodies taking the Giemsa stain have been reported in a number of viral and rickettsial ocular infections occurring in animals In human

conjunctivitis due to Newcastle virus of fowl basophilic cytoplasmic inclusion bodies (on Giemsa) have been noted.

Bacteria and fungi Scrapings are frequently more valuable than smears for the recognition of and evaluation of bacteria and fungi. Better specimens and preparations are often obtained. Bacteria, particularly the gonococcus but others as well, may be demonstrated to be proliferating on the epithelium (especially the bulbar portion) before they are found in the secretion. Fungi such as the Streptothrix in the coccoid form may be demonstrated in neutrophiles in the absence of obvious secretion. It was erroneously believed until recently that only bacteria that were epithelial cell parasites were pathogenic. Usually recognition of the organism involved may be accomplished on morphology alone; if needed a Gram stain of the scraping can be done (table 4). In the two most common forms of blepharitis associated with chronic conjunctivitis, i.e. staphylococcic blepharitis and seborrheic blepharitis, eyelid margin scrapings offer an excellent means of diagnostic differentiation. In the staphylococcal variety cocci and neutrophiles are found; in the seborrheic form budding yeasts (*Pityrosporum ovale*) are seen.

CLINICAL AIDS

Bacterial Conjunctivitis

The precise differentiation of allergic conjunctivitis from conjunctivitis due to bacterial infection requires laboratory investigations; usually smears and scrapings suffice. Clinically, bacterial conjunctivitis may have an incubation period of from two to five days. The reaction almost always papillary generally involves the lower conjunctiva more than the upper in infections with the Staphylococcus, pneumococcus and Streptococcus. In gonococcal conjunctivitis the upper lid may show marked inflammatory changes. With *H. koch weeks* or *H. influenzae* infections the bulbar conjunctiva is often markedly inflamed. Both Koch Weeks and pneumococcal conjunctivitis are often accompanied by conjunctival hemorrhages. It is incorrect to assume that a Morax Axenfeld infection is present on the basis of dermatitis of the medial and lateral canthal regions; such phenomena are often the result of staphylococcal invasion. Depending on the severity of the infection and the resistance of the patient, the inflammatory response may be frankly purulent, mucopurulent or only mucoid. Although the gonococcus and the meningococcus generally evoke the most severe hyperacute purulent discharges, other bacteria may also do so. Similarly, while membranous as well as pseudomembranous conjunctivitis when due to bacterial infection is usually the result of diphtheritic or streptococcal infection, many other bacteria may cause membranous reactions. Corneal complications in general are uncommon. When they are central, gonococcal

or diphtheritic infection may be suspected if they are marginal. Staphylococcus, Koch-Weeks bacillus and Morax-Axenfeld infection are likely causes. Preauricular lymphadenopathy may be present in bacterial conjunctivitis but the glandular enlargement is never as great as in viral infections or Parinaud's oculoglandular syndrome with the exception of tularemic conjunctivitis. In chronic conjunctivitis (usually due to staphylococcal infection) an associated blepharitis and superficial punctate keratitis, as mentioned in chapter 4, often provide valuable diagnostic information. Antibacterial agents are usually so successful in the treatment of acute bacterial conjunctivitis that indications as to the basic nature of the affection are at times almost self evident.

Viral Conjunctivitis

The early recognition of most types of viral conjunctivitis is of the utmost importance epidemiologically, if less so therapeutically. Even if we lack specific agents in all forms of viral infections of the conjunctiva except those due to the chlamydozoaceae (trachoma, inclusion conjunctivitis and lymphopathia venereum), prompt diagnosis to prevent spread to other patients and to ourselves is urgent.

The chlamydozoaceae. In *trachoma* the characteristic findings of papillary and follicular inflammation of the upper conjunctiva with usually associated pannus of the superior cornea and punctate keratitis easily differentiate the infection from all allergies except vernal conjunctivitis. This is elaborated in chapter 8. Inclusion bodies are found in scrapings early in the disease. Excellent responses to the use of sulfonamides and tetracycline antibiotics occur.

Inclusion conjunctivitis predominantly involves the lower conjunctiva. In the newborn it need not have the follicular character it does in the adult. Mucopurulent discharge occurs. Preauricular adenopathy is moderate. Inclusion bodies are demonstrable. A characteristic history is obtained in adults of exposure to swimming pools, stagnant lakes, gynecologic operations, or even eye-to-eye transmission. In the newborn, where the source of infection is the mother's cervix, the affection begins on the seventh to the fourteenth day of life. The cornea is rarely involved. Dramatic subsidence of the infection, which may last for many months if untreated, occurs in a few days with sulfonamides and tetracycline derivatives. Corticosteroids aggravate the disease.

Epidemic keratoconjunctivitis. Early in the course of this infection chemosis of the lower lid conjunctiva with mucopurulent discharge may so dominate the picture that it may be confused with an acute atopic conjunctival reaction. Later the presence of follicles and severe pseudomembranes, the characteristic corneal infiltrates, both epithelial and subep-

thelial (non staining), secondary iritis watery discharge with mononuclear exudates on scrapings and moderate preauricular lymphadenopathy all should easily differentiate the entities In some epidemics corneal complications did not occur The varying picture that epidemic keratoconjunctivitis manifests at different times may indicate that the disease is not a single entity but arises from several related viruses There is no specific treatment

Beal's conjunctivitis This form of acute follicular conjunctivitis of the lower lid is difficult to differentiate from epidemic keratoconjunctivitis except on the basis of serologic tests for immune bodies Clinically its tempo is much milder and the cornea is uninvolved There is no specific treatment Preauricular lymphadenopathy occurs The infection is believed by some to be related to EKC Infection may arise from swimming pools

The adenoviruses The occurrence of other acute types of viral conjunctivitis as a result of infections with the adenoido pharyngeal conjunctival (APC) viruses is now accepted Characteristically the clinical picture resembles that of other conjunctivides due to viruses of small particulate size There is involvement of one or both eyes incubation for five to ten days catarrhal or nonpurulent discharge predominantly lower lid involvement often follicular preauricular lymphadenopathy constitutional symptoms (malaise pharyngitis fever), frequent spread via swimming pools self limited character formation of neutralizing antibodies and lack of specific therapy Early outbreaks were considered Greeley disease Most instances of epidemic pharyngoconjunctival fever in children are due to adenovirus type 3 types 2 3 6 and 7 have been encountered in sporadic cases Various strains of adenovirus type 8 appear responsible for the occurrence of epidemic keratoconjunctivitis (6) The adenoviruses may prove to be responsible for other viral infections such as Beal s conjunctivitis

Herpetic conjunctivitis Primary herpes simplex infection of the conjunctiva may give rise to an acute often follicular unilateral conjunctivitis This may be so severe that conjunctival necrosis occurs Herpetic lesions of the eyelids may likewise be present Preauricular lymphadenopathy occurs If dendritic lesions appear on the cornea in the course of the process the diagnosis of herpes simplex infection becomes more readily apparent Scrapings of the conjunctiva may show mononuclear cells Such primary infection usually occurs in a child whose parent has just previously manifested herpes labialis However it may develop in young adults (fig 44) Since such a picture especially if the eyelids are involved may simulate an acute allergic dermatoconjunctivitis or erythema multiforme its recognition is important Corticosteroids which are valuable in the latter two conditions are entirely contraindicated in herpes simplex infections



Fig 41 Primary herpetic conjunctivitis Patient was apparently infected by her husband who had active herpes labialis Note herpetic lesions of upper lid margin with considerable edema and the acute necrotic inflammation of the lower bulbar conjunctiva A few days later follicular conjunctivitis and a typical dendritic keratitis developed The sequence of events and clinical appearance was that of *primary* herpetic infection (courtesy of Dr A Turtz)

THE OCULO MUCO CUTANEOUS SYNDROMES

The group of interesting syndromes best described under the above name is of obscure etiology Several of them may be allergic in origin, others do not appear to have any allergic component (7)

Erythema Multiforme and Stevens Johnson's Disease

Erythema exudativum multiforme was first described by Hebra in 1866 He gave this name a good one to a condition characterized by sharply defined erythematous patches associated with an edematous exudate having a symmetrical distribution on the hands the forearms and the back of the neck and spreading to the face calves and mucous membranes The disease is essentially a recurrent but benign affair It may be associated with malaise and fever

Oral lesions occur often before the skin is involved and usually start as vesicles which break down to leave large raw areas with ulceration blood crusting and fissuring Pseudomembranes occur These lesions are found on the lips the buccal mucosa the tongue the palate the pharynx

and the bronchi Other mucous membranes such as the vagina and the urethra may be involved but the ocular conjunctiva is the most important of all because of the disastrous sequelae that may occur in a severe type of erythema multiforme known as Stevens Johnson's disease

While Hebra in his original description in 1866 cited a rare variant with severe stomatitis and purulent conjunctivitis the reporting by Stevens and Johnson in 1922 of their two classic cases (8) dramatically focused attention on the eyes in this condition and was followed by a number of similar cases reported by others Where in the usual type of erythema multiforme mild catarrhal conjunctivitis is noted with lesions similar to those occurring on other mucous membranes here a severe purulent form of conjunctivitis occurs In the past this often resulted in corneal ulcers that perforated with complete loss of vision This bleak prognosis has now been modified by steroids and better antibacterial therapy Less commonly a pseudomembranous or membranous conjunctivitis occurs with potentially serious results Here adhesions of the lids to the eyeball (symblepharon) and corneal infection eventually occur due to lack of protection and dryness of the cornea

Stevens Johnson's disease differs from erythema multiforme in that it is a nonrecurrent acutely febrile and occasionally fatal condition with pulmonary involvement in twenty five per cent of the cases While the genitalia and skin are involved the lesions are more hemorrhagic and the



FIG 45 Erythema multiforme (Stevens-Johnson) acute reaction [illegible] penicillin therapy (Theodore (7))



FIG 46 Left eye of same patient as in fig 45 acute hemorrhagic exfoliative dermatitis and pseudomembranous conjunctivitis (Theodore (7))



FIG 47 Erythema multiforme (Stevens-Johnson) end results with severe scarring of conjunctiva due to sulfonamide drug allergy (courtesy of Dr B Friedman)

palms and soles are generally not affected Furthermore in the eyes Stevens-Johnson's disease involves the lid margins and cilia while erythema multiforme does not according to Braley (9)

Some of the most severe instances of Stevens Johnson's disease (figs

45 and 46) and erythema multiforme we have encountered appeared to occur as a result of therapy with drugs such as sulfonamides (fig 47) and penicillin On that basis drug allergy may play a role in the causation of the disease The usually beneficial effects from the adequate use of systemic steroids and corticotropin in conjunction with the covering action of adequate amounts of those antibacterial agents for the eyes not likely to result in further drug allergy, support this viewpoint

Reiter's Syndrome

The symptom complex known as Reiter s disease is assuming increasing importance not only because it is being encountered more frequently but also because of the severe disabilities that may follow At the present time the cause of the condition is unknown and a great deal of confusion *still exists as to exactly what constitutes the disease Even the name is* undeserved Generally Reiter s syndrome is initiated by an abacterial urethritis followed by transient mild conjunctivitis (less often keratitis iritis and secondary glaucoma occur) and later by severe polyarthritis In 1916 Reiter described a case following acute dysenteric symptoms Actually the association of dysentery with conjunctivitis and arthritis was noted fifty years previous to that while the classical symptom complex of urethritis conjunctivitis and arthritis was described in considerable detail as long ago as 1818 by Sir Benjamin Brodie (10) At present cases in which only part of the triad is present in association with skin or mouth lesions are also included by some authors under the heading of Reiter s disease Thus many reported cases appear very similar to erythema multiforme and Behcet s syndrome In fact according to some all of these syndromes may be variants of the same disease

Etiology Many microorganisms have been incriminated as the cause *of the syndrome but none has withstood the test of time* Currently L organisms of the pleuropneumonia group and the virus of inclusion conjunctivitis (cause of nonspecific urethritis) are mentioned most frequently However others have found all studies including bacterial viral and animal inoculation to be completely negative Paronen *(11) reported* three hundred and forty four cases of Reiter s syndrome which occurred following an epidemic of Flexner type dysentery in 1943 and 1944 In this study women and even children suffered from Reiter s syndrome whereas it had hitherto been described only in young adult males *between the ages of* nineteen and thirty eight years Paronen concluded that the dysentery bacillus seems to be the causative factor even in patients in whom no dysenteric infection can be demonstrated by clinical means However there are many patients in whom no evidence for dysenteric *infection can be* found in stool cultures and agglutination reactions

Harkness (10) has reported seven cases of Reiter's disease in which, [illegible]thral [illegible] four [illegible] We have not been able to find inclusion bodies in the conjunctival scrapings at the height of the conjunctivitis in any patient

Clinical course The syndrome is ushered in by a bacterial urethritis usually of transient nature Generally within a few days conjunctivitis occurs The intensity of the conjunctival reaction may vary from minimal to hyperacute, with a great deal of discharge It rapidly becomes bilateral The conjunctivitis is essentially self limited, subsiding in about a week but is dramatically affected by the local use of corticosteroids Other less common sites of ocular involvement include the cornea and the uvea The keratitis that occurs is generally superficial, mild and transient Non granulomatous iridocyclitis may be mild or very severe and may be complicated by secondary glaucoma

The acute polyarthritis that occurs a little later in the course of the disease (usually a few days after the conjunctivitis has begun) causes most of the disability The large joints of the upper and lower extremities are involved—usually the knees and ankles There may be fever Permanent joint changes may occur on occasion so that the arthritis must not be taken lightly

Reiter's syndrome is usually self limited and subsides within four to six weeks Recurrences are infrequent but when they occur they may be more severe than the original attack The second attack sometimes is limited to arthritis or urethritis

Two patients presenting the full classical picture of Reiter's disease afforded opportunities for both etiologic and therapeutic investigation In each instance the patient was a young man in his twenties with a history of recurrent attacks of the disease One was suffering from the sequelae of severe iritis and secondary glaucoma as a result In each case the present episode was ushered in by transitory abacterial urethritis followed by muco purulent conjunctivitis (fig. 48) (responding to local instillations of cortisone) and then by severe incapacitating polyarthritis involving the larger joints such as the knee the ankle (fig 49) and the wrist Etiologic studies of the urethra the conjunctiva and the involved joints were all negative these included viral and bacterial cultures Penicillin Aureomycin and Terramycin for long periods of time proved ineffective in each case Both patients *remained febrile and bed ridden due to the polyarthritis* In one however hydrocortisone was injected into the knee joint with rapid subsidence of the involvement in that joint Dramatic improve

with the ineffectiveness of the antibiotics and the sulfonamides, is evidence against a viral or bacterial etiology, and might suggest an allergic basis for the syndrome, although there is no direct evidence as yet at hand

Behcet's Syndrome

Behcet's syndrome is a systemic disease observed in young persons It is characterized by recurrent attacks of iritis, or iridocyclitis with hypopyon associated with aphthae in the oral cavity and ulcerations of the genitalia

The name of "triple symptom complex" was given to this condition by Behcet in 1937, although he was not the first to describe it Cases had been reported as early as 1908 Since Behcet's report (12) however, a number of other papers have appeared and Behcet's name has become associated with the symptom complex Outstanding among these papers are those of Curth (13, 14) who has made a very intensive study of the disease

The oral lesions. These consist of variously sized and shaped aphthous ulcers which are painful They occur on the lips, the tongue the buccal mucosa the hard and soft palates, and the tonsils The bases of the ulcers are covered with grayish exudate, and their margins are surrounded by a red halo The ulcers may vary from one to five or more millimeters in size they are extremely tender They are recurrent in character They often heal without any scars but sometimes permanent scarring occurs

The genitalia Recurrent ulcerations of the scrotum and of the vulva occur Vulval involvement may result in necrosis with scarring

The ocular changes. The ocular lesions may lead to blindness in both eyes Although involvement of many of the ocular structures has been reported such as conjunctivitis, keratitis and retinitis the important changes occur in the uveal tract Here early inflammatory signs often apparently of little significance, progress inexorably over a period of years until blindness ensues There are exceptional cases in which the ocular inflammation subsides spontaneously and healing occurs

If one insists on the three classical symptoms for the diagnosis the disease is rare If one accepts those instances in which only two of the three major manifestations occur it is encountered more frequently Moreover, additional recurrent evidences of the disease have been noted aphthous cutaneous lesions thrombophlebitis arthritis and involvement of the central nervous system For this reason Curth prefers the term aphthosis to *Behcet's syndrome*

Etiology. Current thought inclines to a viral causation for this disease which may at times have a fatal outcome Sezer (15) has isolated a virus from the ocular tissues in three patients suffering from Behcet's disease





Fig 48 (*abo e*) Re ter s synd ome a ute mucopuru lent con unct t s
Fig 49 (*below*) Re te s syndrome acute arthr t s of ankle

ment occurred in both cases within a day after the systen ic admin strat on of cortisone was begun Symptoms ret irne l v l en it was d scont nued

Tl ese st i l es supp ort tl e exp er nces of otl ers tl at cortico tero ds an l cort cotrop n are of v l e in Reiter s d sease Occasionally only intra venous ACTH is effect ve The excellent response to tl ese agents coupled

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Whether this is conclusive evidence of the viral etiology of the condition remains to be determined

Treatment In general corticosteroid therapy appears ineffectual characteristic attacks have been observed during the course of such treatment Antibacterial agents appear of even less value The use of repeated vaccinations and gamma globulin to increase nonspecific viral immunity constitutes another therapeutic approach

Ocular Pemphigus (Essential Shrinkage of the Conjunctiva)

The name of pemphigus has unfortunately been applied to so many different conditions in which bullae or blisters occur that considerable confusion has resulted It would be best to reserve the term pemphigus for the almost invariably fatal chronic disease characterized by bullae which we call pemphigus vulgaris and for its less frequent variants such terms as *pemphigus foliaceus and pemphigus vegetans* In fact acute pemphigus appears to be an entirely different disease (7)

Pemphigus vulgaris occurs in middle aged persons mostly Jewish Despite remissions it progresses fatally Mucous membrane involvement with *bullae occurs in most cases oral lesions are always noted* in these cases and conjunctival lesions are seen quite frequently In the mouth a rather widespread eruption of more or less confluent blisters or remnants of bullae is found In pemphigus vulgaris an area is involved by a bulla it ruptures *and then the area heals Then other areas are affected* Thus scarring does not appear to occur in the conjunctiva in pemphigus vulgaris—a matter of considerable importance as it is the major characteristic of the so-called ocular pemphigus

The use of corticosteroids often in exceedingly large doses may prove of great palliative value in pemphigus vulgaris sometimes halting the process

It is our impression that to term what has been aptly called essential *shrinkage of the conjunctiva a form of pemphigus* is both incorrect and misleading In this condition (ocular pemphigus) a situation entirely different from pemphigus vulgaris exists While occasionally vesicles are seen in the conjunctiva even though they rupture there is no healing of *the process What starts as a severe conjunctivitis* progresses inexorably through the stage of membrane or pseudomembrane formation (fig 50) to complete adhesion of the eyelids to the eyeball (symblepharon) This eventually results in blindness due to corneal involvement because of drying and exposure of the cornea and is brought about by subepithelial scar formation in the conjunctiva rather than by any superficial process Epithelial scrapings of the conjunctiva reveal eosinophiles

Accompanying the eye changes other mucosal lesions occur mainly



Fig 50 Ocular pemphigus (essential shrinkage of the conjunctiva) early involvement with marked pseudomembrane simulating acute erythema multiforme and other types of acute conjunctivitis with pseudomembrane formation Months later typical scarring with shrinkage became apparent (Theodore (7))

oral as well as nasal and respiratory The blisters here ordinarily heal without scarring but scarring similar to that in the eyes has been reported resulting in laryngeal esophageal and rectal strictures The vermilion border is never involved unlike pemphigus vulgaris Since the condition is not fatal the relentless progression of the ocular picture finally results in painful blindness Women are affected more than men In contrast to pemphigus vulgaris which affects Jews predominantly ocular pemphigus appears to occur in Jews only very rarely

The beneficial results of steroid therapy in pemphigus vulgaris do not occur in essential shrinkage of the conjunctiva or ocular pemphigus While an allergic component may play a role in true pemphigus there is no evidence that it does so in the ocular variety

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10

ALLERGY OF THE EYELIDS: GENERAL CONSIDERATIONS

Like its conjunctival lining the eyelid proper is often the site of allergic reactions In fact, such allergies occur so commonly that they would appear to constitute, at least statistically the most important form of ocular allergy encountered in clinical practice Their consideration was deferred until now, not in any attempt to minimize this importance but because we felt that our purposes were best served by first presenting a complete exposition of allergic conjunctivitis as the unusual opportunities the conjunctiva affords for the observation and understanding of all types of allergic reactions offers such an excellent introduction to the consideration of ocular allergy in general

In a broad sense the eyelids represent a transitional structure comprising on the one hand the conjunctiva and on the other the skin of the eyelids with the lid margin a relatively unique zone, in between At this allergic crossroad, because of the intimate relationship of these three areas allergies of both the conjunctiva and the eyelids often overlap and occur at the same time The most important such combined reaction is allergic dermatoconjunctivitis—where although the conjunctiva is generally the focal point of the allergic contact reaction the skin of the eyelids soon becomes involved In addition to this contact type of allergy certain anaphylactic atopic and microbial sensitivities especially those involving the glandular structures of the lid margin may likewise assume a diffuse character evoking reactions at all three points On the other hand where the eyelid skin is the original site of contact as for example in allergy to cosmetics spread to the conjunctiva is the exception not the rule so that the reaction is limited to the skin only

CLASSIFICATION OF ALLERGIES OF THE EYELIDS

The classification of allergy of the eyelids offered in table 5 is useful for a panoramic understanding of the subject in general. It will be adhered to in the chapters dealing with allergic and related reactions of the eyelids which follow immediately. Allergic dermatoconjunctivitis already has been fully dealt with in chapter 5.

TABLE 5

Allergy of the eyelids

1. *Anaphylactic and atopic allergy (immediate)*
   a. Allergic edema (urticaria, angioneurotic edema, serum sickness, insect bites), drugs, animal sera, etc.
2. *Contact allergy (delayed)*
   a. Allergic dermatoconjunctivitis: drugs, chemicals
   b. Eczematous contact dermatitis: cosmetics, drugs, chemicals, apparel
3. *Microbial allergy (delayed)*
   a. Infectious eczematoid dermatitis
      1. Bacterial: Staphylococcus, Streptococcus
      2. Fungal: trichophytosis, moniliasis
   b. Infections of the lid margin (usually staphylococcal)
      1. Blepharitis
      2. Meibomitis
      3. Hordeolum
      4. Chalazion

11

ALLERGIC EDEMA OF THE EYELIDS

The accumulation of edema fluid in the eyelids as a result of an allergic reaction is with few exceptions a manifestation of an atopic or anaphylactic reaction Even in those instances in which the allergen is microbial or in the rare case in which contact appears to be the cause of the reaction the mechanism seems to be of the immediate type rather than the delayed Most of the time allergic edema of the eyelids arises in the course of generalized allergic reactions such as urticaria angioneurotic edema serum sickness, drug reactions general bacterial sensitivities and parasitic infestations Sometimes however the reaction occurs in response to local exposure to such causes as insect bites sunlight and contact agents

Edema of the eyelids allergic or otherwise often assumes an importance more apparent than real because of anatomic factors peculiar to the orbital region Minor edema hardly noticeable elsewhere soon becomes very marked here and sometimes alarming not only because of the extreme laxity of the skin and subcutaneous structures of the eyelids but also because fascial attachments on all sides of the orbit prevent the lateral extension of the edema to the adjacent forehead or cheek Since the only path for the accumulating fluid is forward protruding bags of edema fluid often occur Thus the picture may be magnified out of all true focus The extreme edema of the eyelids that may occur due to a relatively minor hordeolum or stye is well known

The specific causes of allergic edema of the eyelids are considered in the discussion of urticaria and angioneurotic edema which follows immediately

URTICARIA AND ANGIONEUROTIC EDEMA OF THE EYELIDS

Edema of the eyelids is an essential feature of most instances of angioneurotic edema and often is prominent in urticarial swellings Indeed a special predilection for involvement of this site appears to exist in these

two related conditions Etiologically, as well as pathologically urticaria *and angioneurotic edema are essentially manifestations of the same process* They may both occur in the same person at the same or different times and they appear to be the results of the same causes The wheal in each case is made up of exuded serum containing eosinophiles and other leukocytes It is believed that histamine like substances cause the dilatation of the local lymphatics and blood vessels resulting in edema Urticaria or hives are wheals of an essentially acute evanescent character *limited to the dermis only occurring in groups tending to coalesce over* many parts of the body Their extremely pruritic character is thought to be due to involvement of superficial cutaneous nerve endings (1) Angioneurotic edema the more dramatic and more serious manifestation has a deeper involvement affecting the subcutaneous tissues and mucous membranes especially of the viscera Its predilection for the face especially the eyelids and lips is marked The edema may subside in several *hours or last for days attacks may recur at frequent* or prolonged intervals Visceral involvement especially fatal edema of the glottis is common in the rare hereditary form of angioneurotic edema Other areas that may be involved in angioneurotic edema include the mucosa of the upper respiratory tract the bronchi the gastrointestinal and urogenital tracts and the brain and its coverings Papilledema has been described (2) The broad scope of the ocular manifestations of angioneurotic edema is only now being accepted Conjunctival corneal and especially uveal involvement with secondary glaucoma (see chap 19) are sometimes of great magnitude

While most instances of urticaria and angioneurotic edema appear to be clear cut manifestations of the immediate form of *allergy the mechanism* at other times is far from definite and may not always be truly allergic The correlation of an atopic history with urticarial manifestation is not as high as is found in other types of allergy such as hay fever and

eruptions *have been recorded Urticaria occurs mostly in* women between the ages of 20 and 40 Like other atopic manifestations of allergy the reactions may occur in a few minutes after exposure to the exciting substance Eosinophilia is less apt to occur

Certain specific causes of urticaria and angioneurotic edema *are considered* below After them other possible causes are discussed In very many patients no definite basis for the reaction especially in chronic *recurrent cases is ever established*

Allergic Factors

Foods A common cause of urticarial reactions is food Acute varieties appear to be caused primarily by fresh fruits and vegetables (1) (particularly strawberries, bananas oranges raspberries peaches cantaloupes watermelons and tomatoes), as well as shell fish nuts and chocolate Other types of fish such as sardines may also cause acute reactions Chronic urticaria is usually due to common basic foods such as eggs wheat milk pork onions celery and other common vegetables particularly green peas potatoes and corn Alcoholic liquors may act as precipitating factors in urticarial eruptions perhaps by increasing the absorption of other ingested allergens

Drugs Some allergists (3) feel that since the introduction of antibiotics drugs have become the most common cause of urticarial reactions While hives have occurred following the use of a large variety of drugs and simple chemicals certain ones appear particularly liable to result in urticaria and angioneurotic edema These include acetophenetidin aspirin aminophylline antipyrine arsenicals atropine barbiturates bromides cinchophen digitalis ephedrine emetine iodides morphine and other opium derivatives penicillin and other antibiotics phenolphthalein quinine and sulfonamides Even chlorinated drinking water has caused such reactions (4) With the exception of penicillin most antibiotics cause only infrequent minor allergic reactions According to Siegal (5) there are 5 types of penicillin allergy 1) the common delayed form simulating serum sickness in which urticaria is the most common manifestation 2) uncommon accelerated and immediate reactions sometimes anaphylactic in nature 3) hyperergic cutaneous vascular and visceral phenomena 4) common erythematovesicular or id like reactions activating presensitization induced by previous fungous disease of the skin and 5) contact dermatitis Anaphylaxis sometimes fatal may be avoided by immediate skin tests

Various injected substances especially those antisera and antitoxins derived from horses and other animals may result in edematous reactions as well as cause serum sickness These may also occur following human blood transfusions Organ extracts such as liver insulin and other hormones both natural and synthetic also give rise to urticarial reactions Vaccines may likewise do so

Insect bites Insect bites and stings are capable of causing typical atopic and anaphylactic reactions in sensitive individuals On rare occasions fatal anaphylaxis may occur especially following stings by bees and wasps in previously sensitized persons Local swelling of sometimes marked proportions as well as generalized urticaria and angioneurotic edema are not uncommon Edema of the eyelids due to insect allergy usually but

not always, is the result of a local process The allergy appears to be due to the protein of the insect itself rather than the venom of its sting or bite Sometimes heroic measures are needed to control insect anaphylaxis Desensitization with antigen prepared from whole adult insects is useful where indicated It should be remembered that allergy to insects may also arise from scales or dust on the wings or body of insects According to Etter (6) the more important offending insects include wasp bee ant mosquito caddis fly, May fly, flea, bed bug house fly, body louse, deer fly chigger locust mushroom fly, citrus fruit fly beetle water flea mite moth scabies, yellow jacket and Mexican kissing bed bug

Inhalants In general, urticarial and angioneurotic reactions from inhalants are extremely rare However, a large number of inhalants such as feathers, cotton silk dust, animal dander, pollen and orris root (Fig 51) have on occasion been responsible for such reactions Hematogenous distribution to the skin probably occurred after absorption through the respiratory tract Extreme instances of this type of reaction include a case in which the mere smelling of the odor of fish resulted in urticaria (7) Inhaling buckwheat caused hives in a woman with food allergy to this product Perfume ragweed pollen, the fumes of fresh paint and the by-products of burning cigarettes have also been known to cause such reactions

Contactants Contact urticaria is rare Reactions have been reported however, from cat hair caterpillar hair, sheep wool silk orange grape fruit, lemon, carrots, wheat flour, corn starch egg white pollen horse dander lip stick (in a man immediately after being kissed by his wife who had just applied a new brand) and to various drugs (7) In all of these instances the reaction was limited to the site of contact

Microbial allergens Allergenic or toxic products arising from foci of bacterial infection or during the course of other infections such as the common cold or from infestations with fungi helminths or protozoa appear capable of causing urticarial reactions about the eyelids While the exact mechanism may be controversial in those cases where the elimination of the causative agent results in disappearance of the urticaria or angioneurotic edema some such etiologic connection must be assumed In this regard the urticarial swelling of the lids that occurs in trypanosomiasis is of interest This is a commonly recurring feature in the early stages of the disease but it may also occur in its *terminal stages* According to Habig (8), such swellings are an anaphylactic phenomenon due to acquired sensitivity to the protein of dead organisms Similarly, infestations with round worms and flat worms may cause toxic or allergic urticaria of the eye lids Ascaris Oxyuris both forms of *Ankylostoma duodenale* and *Necator americanus* (ankylostomiasis) and *Trichinella* all are able to cause such

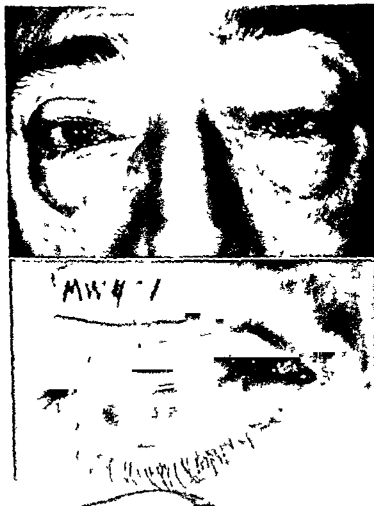


Fig 51 Allergic reactions to orris root may be of either the immediate or the delayed varieties (*Top*) Immediate type of response as a result of inhalant allergy characterized by edema of the eyelids and chemosis occurring within a few minutes after exposure and rapidly controlled by epinephrine (Courtesy of Dr H F Thorpe) (*Bottom*) Allergic der[illegible] face powder containing orris root as a typical delayed type of contact allergy (Courtesy of Dr H F Thorpe)

reactions Only in filariasis is the swelling due to direct invasion of the eyelids by the parasites However the calabar swellings occurring in one form of filarial disease (onchocerciasis) are believed to be anaphylactic reactions to the toxins of the parasite

An interesting case history most suggestive of allergy to the products of the trichina has been brought to our attention Following very severe trichinosis proved in 1946 by muscle biopsy forty six per cent blood eosinophilia and other manifestations the patient (a physician) has had recurring acute episodes of lid edema so intense as to close the eyes completely, along with alarming asthmatic attacks following the eating of pork products These always respond dramatically to epinephrine indicating their specific allergic (almost anaphylactic) nature The patient eats crisp bacon daily with impunity and on many occasions has eaten other forms of well cooked pork with no untoward sequelae Allergic attacks occur usually from unsuspected pork products like sausages and frankfurters Since he has manifested an extreme immediate reaction on skin test to Trichinella antigen (within two minutes after intradermal injection his entire forearm became swollen on one occasion) the likelihood is that this patient is allergic to minute amounts of Trichinella proteins in the varying pork products to which he is unwittingly exposed rather than the pork itself Intradermal injection of pork antigen gave only the slightest reaction while Trichinella antigen in 1 1 000 000 dilution was strongly positive when the patient was last tested in 1957 The Trichinella



FIG 52 Reaction from exposure to sunlight Only area to the left of the eye was pre ent no sunburn This occurred on a number of occasions

reactions which this patient manifests on different occasions after eating small amounts of pork products would indicate the high percentage of pigs with trichiniasis

Physical allergy. Physical agents may cause urticaria and angioneurotic edema either as a result of a specific allergic reaction or as a precipitating influence if other allergy is present Such allergic reactions to cold may be of two types a local contact reaction or a general reflex one In the first type of reaction a localized edema occurs at the site of contact In the reflex type urticaria occurs at sites distant from the exposed portion of the body The mechanism of such cold allergy is usually considered to be a histamine release or else a formation of a histamine like substance at the site of exposure Contact or local reactions to heat appear rare but reflex reactions seem more common Reactions from light are essentially localized contact phenomena For this reason urticaria of the eyelids is a prominent finding when such reactions do occur Figure 52 shows an example of such a reaction to sunlight

Nonallergic Factors

In a significant number of patients with urticaria and angioneurotic edema no definite allergic mechanism can be demonstrated However certain pathologic conditions of the gastrointestinal tract and abnormal metabolic and endocrine processes apparently play a role in their production either as predisposing factors or by autogenous allergy (7) or through other even more obscure mechanisms In any event when these abnormalities are corrected the edema often disappears

Disturbances of the gastrointestinal tract Gastritis enteritis and colitis have been associated with urticaria and angioneurotic edema In fact it is claimed that the urticaria may involve the gastric mucosa itself Similarly pancreatic insufficiency as well as liver and gallbladder disease may be responsible Constipation is a common finding in urticaria Occasionally hyperacidity appears to be the cause of urticaria but far more often either marked hypoacidity or marked anacidity is a major factor

Metabolic and endocrine disturbances Gout has been associated with urticaria however associated allergies may be responsible Diabetes may on occasion be the cause of chronic recurrent urticaria Menstrual disturbances also may play a role Abnormalities of the thyroid gland are perhaps of more importance especially hypothyroidism although hyperthyroidism is responsible once in a while Hypoparathyroidism has been observed as a cause in one instance

Psychic influences Psychosomatic factors are felt to play an important role in certain types of urticaria and angioneurotic edema particularly of the chronic variety

Treatment

Specific therapy for allergic edema of the eyelids occurring in the course of angioneurotic edema and urticaria is directed towards removing the cause if possible The responsible or suspected food drug or any other substance that might directly or indirectly cause the reaction should be eliminated Desensitization is of value only in those rare instances in which such substances as inhalants or insect allergens are proved to be etiologic factors The removal of possible foci of microbial allergy where feasible should be undertaken with caution but may sometimes prove dramatically effective

Nonspecific treatment begins with the use of antihistaminic drugs which in these disorders are especially valuable When necessary large doses may be given or intravenous administration may be performed Ephedrine and related drugs may be valuable where antihistaminic alone are ineffectual Epinephrine is of course the drug of choice when anaphylactic reactions or edema of the glottis occur However even in chronic cases it often affords relief in patients unresponsive to other medicament Steroids are especially valuable in severe acute reactions such as those caused by drugs Here intravenous corticotropin (ACTH) may be necessary for immediate therapy later oral corticosteroids suffice Their use in chronic urticaria is generally not advocated

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12

ECZEMA OF THE EYELIDS DUE TO CONTACT ALLERGY

The skin of the eyelids is particularly apt to become inflamed, producing the clinical picture known in a broad sense as eczema. Until relatively recently the various forms and causes of such dermatitis were neither distinguished nor understood, and management, at best difficult, was of necessity based on a general nonspecific approach. Since this often proved unsatisfactory, ocular eczema became an entity toward which many physicians assumed a fatalistic if not a defeatist attitude. When the vast scope and many manifestations of hypersensitivity began to be appreciated, it was realized that most cases of ocular eczema were allergic in nature, occurring as the result of contact allergy. Then, as often happens, the pendulum swung to the other extreme. The dramatic cures that followed when the offending agent was discovered and eliminated gave momentum to the general impression held by many physicians that ocular eczema is always allergic in nature. Actually, it appears that while contact allergy is the cause of most instances of acute dermatitis of the eyelids, other causes do exist (1) and must be differentiated if treatment is to succeed. In each instance the management is entirely different; incorrect therapy based on the wrong diagnosis not only will yield no benefit but at times may result in serious aggravation of the original dermatitis. In this chapter eczema of the eyelids due to contact allergy will be considered; the more important of the other causes are discussed in the next chapter.

It is easy to appreciate in this era of vast industrialization and widespread home use of so many new chemicals, drugs, synthetics and processed substances that contact dermatitis, a disease of civilization, appears to be the most common skin disorder encountered. What must be remembered

however is that many of the e contact reactions are not allergic in nature but instead are due to direct primary irritation In fact more occupational dermatoses are believed to arise from such irritation than from allergy However in certain locations such as the eyelids contact reactions are usually allergic in character

The tendency has arisen to reserve the term eczematous dermatitis for those lesions due to contact or other allergies and to use the term eczematoid dermatitis for reactions of nonallergic origin that are similar in appearance Here the term eczema is used as defined by Sulzberger (2) to describe any skin reaction situated principally in the epidermis characterized grossly by several of the following erythema papulation vesiculation oozing crusting scaling thickening pigmentation and itching regardless of the cause or the mechanism of production

Certain factors such as excessive dryness (tending to cause fissures) extreme greasiness (tending to maceration) and inability to neutralize alkalies (possibly due to lack of fatty acids) predispose to skin reaction in general The skin of the eyelids however is particularly susceptible to inflammation for several special reasons First its fine texture and extreme thinness readily permit minor traumatization and the penetration of noxious substances of all types Second due to their location the eyelids are especially exposed to physical trauma (rubbing heat sun wind and ocular secretions) and to various drugs and chemicals applied elsewhere on the head and face Thus although a facial cream or hair tonic is not directly applied to the eyelids the eyelids may eventually prove to be the only site of the eczema as even a minimal amount of the irritant indirectly contacted by means of a pillow case during sleep or the fingers is able here to penetrate sufficiently to cause the reaction in contrast to its inability to penetrate the thicker and stronger skin where it was originally applied so generously Similarly the skin of the eyelids often reacts to bacterial products or ocular medicaments occurring in tears which would be harmless elsewhere on the skin This special susceptibility of the eyelids holds for both primary irritants and true sensitizers (allergens) indicating a low threshold of irritability rather than a hyperergic state although such irritants are less likely to come in contact with the eye than with other parts of the skin

MECHANISM

The mechanism responsible for the production of contact allergy of the eyelids is basically that of contact dermatitis in general The original sensitization almost always occurs as a result of direct skin contact On occasion allergy would appear to originate from absorption via other

routes such as the ingestion (3) inhalation or injection of eczematogenic allergens especially drugs taken internally It also seems clear that once sensitivity exists cutaneous reactions may occur following exposure by these internal routes This is supported by clinical experiences Experimental evidence however is less conclusive In the guinea pig for example while direct application of poison ivy extract has resulted in the experimental production of skin sensitivity (4) other routes such as intramuscular, intravenous and intraperitoneal injections were not successful Sensitivity to arsphenamine was produced in this animal by intracutaneous injections but could be inhibited by intracardial injections of the same antigen performed within twenty four hours (5) Landsteiner and Chase (6) and Strauss and Spain (7) on the other hand were successful in provoking contact allergy following intraperitoneal injections of simple as well as conjugated sensitizers It should be pointed out however that humans react differently from experimental animals in regard to contact allergy so that certain discrepancies between clinical and experimental observations may thus be explained

After an incubation period of generally from seven to ten days (although it may be as long as twenty-four) generalized hypersensitivity becomes established Allergic reactions which may then occur follow the usual pattern of the delayed type of allergic response requiring hours to days (usually twenty four to forty eight hours) after antigen contact for their appearance As distinguished from the immediate form of allergic response

It appears rather definite that the site of the reaction is cellular rather than humoral According to Sulzberger (2) the shock tissue is always the epidermis whether the route of exposure is external or internal In contradistinction he believes that in atopic dermatitis where protein allergens are involved the shock tissue is usually the cutis rather than the epidermis

The histologic lesion is essentially epidermal Both intracellular and intercellular edema (spongiosis) occur starting in the superficial portion of the prickle cell layer and resulting in actual intraepidermal vesicles accompanied by vasodilation edema and lymphocytic exudation in the upper cutis This response like the microscopic findings in other forms of allergy is essentially non specific and indeed the same as those caused by the application of primary irritants to the skin However Nexmand (8) appears to have demonstrated an interesting difference between the cellular content of the blister fluid from allergic patch test reactions and

that of *primary irritants* The allergic exudate was predominantly mononuclear, containing lymphocytes and monocytes, the exudate in primary irritation proved essentially polymorphonuclear

From various types of transplantation experiments using very superficial skin grafts Haxthausen (9) has concluded that the eczematous allergic reaction is not a stationary condition Normal skin transplanted to a sensitive host acquires the latter s sensitivity within a few days indicating that the allergic individual produces a factor which penetrates into the skin and makes it sensitive On the other hand the sensitive donor skin soon loses its sensitivity when transplanted to a normal recipient Even homotransplants in sensitive individuals react negatively until five days *in situ in the new location All this implies that the factor responsible* for eczematous allergy comes from within the body and he believes it related in some manner to the lymphocytes He thinks that specific antibodies may be produced by these cells just as ordinary antibodies are produced by plasma cells but that there also is the possibility that the *lymphocytes, in a more direct way play a part in the rise of the eczematous* allergic reaction

In line with this thinking all the evidence available would appear to indicate that mononuclear cells both lymphocytes and monocytes carry the theoretical antibodies of contact allergy Passive transfer however by means of the transference of white blood cells from sensitive donors to nonallergic recipients has given so far negative results It seems though that active sensitization of the recipient to the allergen in question is facilitated in some manner by such transfer (10)

The question of the spread of the sensitization was discussed by Grolnick (11) in his study of the mechanism of contact allergy Citing numerous experiments including some of his own while granting that humoral influences *played a role he insisted that the skin itself* was not merely the end point but also the medium in the ultimate establishment of generalized skin sensitivity through direct spread—perhaps by diffusion Rostenberg (12) inclines to the idea that the primitive *reticulum* cell of the cutis and of the regional lymph nodes is responsible for the generalization and perpetuation of the sensitivity

Influence of Heredity

There is no transmission of contact allergy from parent to offspring Atopy generally plays no role at all Although ragweed hay *fever is an* atopic disease contact sensitivity to ragweed oil has been shown to occur with equal frequency in both atopic and nonatopic persons (13) However Landsteiner and Chase (14) have shown that by *selective inbreeding* of guinea pig a strain highly susceptible to skin sensitization can be

developed Certain individuals moreover do seem to develop contact allergies much more frequently than do others

Incidence

The relationship of contact allergy to the concentration of the allergen and the frequency of application was demonstrated by the experiments of Bloch and Steiner-Wourlisch (15) in 1926 For many years it had been thought that contact allergy represented rare individual and innate idiosyncrasies These investigators proved that any individual could be made sensitive to the primrose plant (primula) if one used a concentrated enough extract a sufficient number of times Some persons required more applications than did others The susceptibility of humans to sensitization with certain particularly potent excitants has been listed by Grolnick (11) as follows primula one hundred per cent krameria (a plant extract) eighty seven per cent poison ivy seventy three per cent dinitrochlorobenzene seventy per cent orthoform forty five per cent While studying the flare up reaction or the first visible sign of skin sensitivity Grolnick noted that previously negative areas became positive when the flare up developed after repeated testing This occurred as long as forty three days after the original application indicating that the allergen could stay fixed in the cell for that long a period of time although quantitative tests indicated that most of the excitant has been lost by then

Primary Irritation Versus Sensitivity

In any discussion of the mechanism of contact allergy in general as well as of its demonstration and diagnosis a consideration of primary irritants as compared to sensitizers must be included This has already been done in some detail in chapter 6 as this consideration forms the basis for the concept of drug irritation of the conjunctiva which although relatively uncommon is none the less an important clinical entity Primary irritation of the skin however as a cause of contact dermatitis is by no means rare In fact according to Schwartz (16) as noted previously the majority of occupational dermatoses are actually due to such irritation rather than to true allergy Diagnostically the differentiation of irritation from allergy is an ever recurring problem in this field To complicate things agents that in low concentration prove to be potent sensitizers appear to be primary irritants when applied in higher concentration For these reasons a little repetition and additional information is necessary at this point

Reactive substances coming in contact with the skin may be divided into two classes 1) primary irritants and 2) cutaneous sensitizers Some substances may act in both ways Primary irritants cause an inflam

matory reaction only by direct action and solely at the site of contact Inflammation occurs if the irritant is used in strong enough concentration or in sufficient quantity for a long enough period of time Unlike an allergy the irritation may develop the first time the substance is used The irritant may form a chemical combination with the skin or else abstract one or more of its essential ingredients, such as moisture or lipoids Those substances which enhance physiologic defects that are already present in the skin such as dehydrating chemicals in persons with inherently dry skin are more apt to cause irritation This may explain the importance of primary irritation in occupational contact dermatoses Persons with thin skin are more liable to primary irritation than those with thick skin areas where the skin is delicate are similarly more likely to become irritated Primary irritants may in addition be sensitizers from the start or become sensitizers on intensive use This fact explains some types of reactions that occur where an allergy is superimposed on an irritation

Sensitizers differ from irritants in that they act as true allergens Thus they do not generally cause reactions on first contact In technical after approximately a week the *entire* skin or *all* the mucous membrane will react in a specific manner on further contact either at the original site or elsewhere

Penetration

When one reviews the clinical and experimental information available concerning the frequency and occurrence of cutaneous contact allergy one factor that apparently is common to both allergy and irritation stands out *penetration* of the noxious substance into the skin Anything that allows increased penetration aids in the provocation of allergy anything hindering such penetration will block against allergy at this site Where such protection is lacking and penetration is relatively easy as in the eyelids allergy through indirect or secondary contact as noted previously is especially apt to occur

The term penetration is used to signify entrance of a substance into the epidermis the shock organ in contact allergy, and this is the problem that concerns us here Absorption or deeper penetration into the dermis and eventual entrance into the general circulation is something else Actually most absorption bypasses the outer layers via the skin appendages There appear to be two major barriers to skin penetration 1) the horny layer of the skin and 2) fatty substances on the *skin surface* The horny layer however in a physiologic sense does have gaps in it Furthermore while the waxes and cholesterol esters present are regarded as forming a repellent film actually according to Schwartz and Peck (17) they only delay the

penetration of water and aqueous solutions On prolonged contact emulsion mixtures are formed which then penetrate the horny layer

Injuring the epidermis facilitates penetration Thus experimental removal of the horny layer or rubbing it with glass paper will permit the development of an allergy to a substance in a concentration that produces negative results with normal skin Removing the lipoid film with solvents increases the permeability of the skin Thus some of the principal causes of contact allergy are agents that act in this manner—for example oily substances such as plants and lubricants Similarly any prolonged friction and sweating will aid penetration of the allergen Contact allergy to articles of apparel often arises on this basis Examples of such a mechanism would include allergy where a tight girdle presses the most dermatitis to a tight leather inner band of a man s hat and spectacle and wrist watch dermatitis Dye dermatitis to a colored shirt is prone to occur only in those skin areas where perspiration is intense (18)

Since penetrability is an important factor in contact allergy any skin defect microscopic abrasion unusual thinness of the epithelium or deficient or abnormal glandular secretions will predispose to the reaction Gaul and Underwood (19) have demonstrated how much more frequently mercurial sensitivity follows the application of mercurial products to damaged or broken skin than the use of the same substances on the intact epidermis The ready penetration of certain chemicals may serve to explain why these compounds are more allergenic than others less prone to enter the skin These include lipoid soluble local anesthetics such as tetracaine (Pontocaine) and Nupercaine opium alkaloids heavy metal salts phenol derivatives and hormones as well as vegetable and animal fats such as lanolin so frequently used as ointment vehicles

Immunologic Chemistry

Since most of the antigens that cause contact allergy are nonprotein in nature according to basic allergic concepts they could not of themselves cause reactions According to Grolnick (11) as early as 1907 Wolff Eisner offered another explanation based on the demonstration a year previously by Obermayer and Pick—that the properties of protein antigens could be altered by chemical manipulation Wolff-Eisner suggested that nonprotein chemical compounds caused sensitization by combining with proteins in the body Later work by Obermayer and Pick (1912) and exhaustive investigations by Landsteiner and his co workers (1918 and 1946) confirmed this idea and placed immunologic chemical specificity on a definite basis bridging the hiatus between immunology and chemistry At the present time it appears to be accepted that relatively simple chemicals

combine with body proteins to form conjugates that act as antigens The hapten confers specificity on the conjugate so that the allergy is directed against the chemical and not against the protein This explains why it is inadvisable to substitute a chemically similar drug for another that has resulted in sensitivity Thus after allergy to one sulfonamide has developed another sulfonamide is very likely to cause an allergic reaction However Landsteiner (20) himself has pointed out that while this concept of hapten protein conjugation has been proved beyond question for chemicals of relatively simple constitution a chemical interpretation is not immediately at hand as regards more complex substances that cause sensitivity such as picric acid and quinine He postulates that these substances may be converted in the animal into more reactive compounds

This fundamental work of Landsteiner and his co workers has been confirmed and elaborated by others According to Alexander (21) antibodies have been produced against substances as simple as magnesium oxide calcium chloride and lithium chloride

For the vast majority of chemicals concerned in the production of contact allergy however no such antibodies have been demonstrated Since it is generally accepted that allergy is an acquired specific alteration in the capacity to react brought about by an antibody mechanism and since there is no question that contact allergies are indeed true hypersensitivities this question is of importance In fact unless the concept of an antibody mechanism is included in such a definition certain nonallergic phenomena in which altered reactions occur would serve to confuse the entire problem

According to Rostenberg (22) the most widely held theory for the production and specificity of antibodies is that of stereochemical complementarines It assumes that antigen gets to the site of globulin synthesis and modifies the surface of the globulin molecule electrochemically Such surface modification varies according to the antigen and imparts specificity to the allergy An alternative theory advanced by Burnet (23) assumes that alien protein or antigen causes enzymatic changes in the globulin cells resulting in the production of globulin with a different molecular configuration thus conferring on it specific antibody properties To explain the reaction in contact allergy Rostenberg and Brunner (24) have advanced Burnet s ideas one step further They feel that when similar enzymatic changes occur as a result of antigen contact in cells or systems not concerned with the synthesis of serum globulin while no detectable antibodies are found these altered cells in which adapted enzyme systems have developed are now sensitized and will thereafter react allergically when exposed to antigen They feel that the primitive reticulum cell are not likely to become so affected enzymatically These ubiquitous cells are pre

ent in the cutis as well as in the regional lymph nodes Lymphocytic transformation of such adapted cells or their descendants into epidermal cells would explain the development of generalized skin sensitivity

Interesting and provocative as such speculations are perhaps of more immediate importance to the practitioner are several other aspects of immunochemistry Not only does it appear that certain groups of chemicals are especially allergenic, but that among the various isomers of the very same chemicals great antigenic differences occur (stereoisomerism) For example, those compounds with benzene ring nuclei to which either an NH_2 group or a chlorine atom is attached—especially the ones containing acid groups—have been found to have marked antigenicity So have compounds containing pyrimidine rings Another characteristic that many allergenic drugs have in common is the formation of quinone oxidation products in the body especially quinone diimine This compound when bound to protein, is an exceedingly potent sensitizing agent Foremost among such compounds forming quinones is the dangerous sensitizer and toxic agent paraphenylenediamine Other instances have been reported of substances in themselves not particularly allergenic metabolizing into products that then act as antigens

The role of structural spatial relationship as a factor in the antigenicity of chemical compounds is now well established It was originally shown by Landsteiner (20) that the very specificity of antigens often depends on such stereoisomerism The most important application of this concept concerns those chemicals containing benzene rings in their molecular structure to which NH_2 (amine) or other type of group is attached in the para- or 4 position in the ring Such substances are far more allergenic than are chemicals of similar molecular formulae differing only in the fact that the NH linkage is in the ortho- or 2 position or the meta- or 3 position One explanation of such antigenic disparity as advanced by Rostenberg (25) is not that the ortho or meta drugs are incapable of conjugation with tissue proteins but that they cannot form appropriate conjugates in sufficient concentration within a requisite time The varying allergenicity of different stereoisomers is presumably related to the ease of conjugation of the compound with tissue protein The lack of a proper handle prevents formation of the complete antigen As a result eczema usually does not occur but may do so if exposure is adequate enough

The great significance of such para-compounds in the causation of contact allergy has been remarked upon in chapter 5 In fact Sidi and Mawas (26) consider such chemicals of paramount importance in ocular eczema However para-compounds play such a large role in our own modern environment that it is practically impossible to avoid them So many of the

chemicals contained in foods, cosmetics and dyes or used as drugs, such as sulfonamides and synthetic local anesthetics, are of this structure that our contact with para-compounds is almost constant

Cross sensitizations (that is, allergies to drugs related chemically) are common These include allergies to chemicals containing like groupings—for example, benzamine drugs (benzene ring-containing drugs with amine linkages) and those forming similar types of conjugates Although the use of entirely dissimilar drugs may, at times, appear to result in cross sensitization (possibly because in their metabolic breakdown they attain points of chemical and immunologic similarity), Baer and Leider (10) feel that it is unwise to so label these reactions without more direct evidence

CAUSES

Contact allergy of the eyelids is usually due to the use of cosmetics or ophthalmic drugs Allergy to plants is, however, not uncommon Less often articles of apparel, jewelry, metals, plastics, other chemicals and animal or vegetable products too numerous to mention may cause the reaction In other words, although certain types of substances, because of their frequent contact with the skin of the eyelids cause most allergic dermatitis of the eyelids, any substance whatsoever may, in a susceptible individual result in contact allergy Among the more interesting and rarer causes might be mentioned allergy to carbon paper, to the black ink of newspapers just off the press, the colored inks of the comics or the photogravure and magazine sections of Sunday newspapers in the United States New causes of contact allergy are constantly being reported such as diethyl phthalate (a common ingredient of many insect repellents) and thioglycolic acid and its salts (used in cold-wave lotions and in depilatories)

It is difficult to be certain as to the relative importance of the various contactants causing allergic eczematous dermatitis Most of the literature consists of isolated case reports These, while both interesting and valuable shed little light on this aspect, worse than that, they tend to overemphasize the more bizarre and rarer causes One of the most valuable of the earlier papers is that of Hollander and Baer (27) There are however a few reports available in which large enough series of patients suffering from ocular eczema have been studied to permit the authors to draw certain conclusions in regard to both the causation of the condition and methods of diagnosis While many of these do list cosmetics as the main offender they do so with varying emphasis, due to the fact that they represent studies on different types of people from different countries whose habits [illegible] their allergic propensities Another factor [illegible]port is that the specialist who is [illegible]kely to encounter only the deep

seated problem case not the common variety The usual offenders are immediately thought of by the family physician or even the beautician and generally successfully eliminated Some years ago fingernail polish was certainly the most important cosmetic sensitizer At the present time because every one has been alerted to its importance allergy to it is suspected right away Since such patients never do get to see the allergist the dermatologist or the ophthalmologist the experiences of the specialists may be different from those of the general physician Still another source for conflicting statistical conclusions lies in the fact that specialists in different fields encounter different causes for the allergic reaction It is only natural for the ophthalmologist to see more allergy from drugs he prescribes With these limitations in mind it is worth while going into some detail concerning certain investigations in this field

In 1944 Hazen (28) in a very interesting and compact paper reported his finding in thirty six cases of dermatitis of the eyelids Thirty three patients were women three were men Hazen stressed the importance of the history the use of patch tests the elimination of suspected substances the observation of results obtained and the examination of other parts of the body Like others he pointed out that since the eyelids are so very sensitive patch tests performed on the skin elsewhere might give negative results even if the substance used were the actual cause of the eyelid eczema In fact all methods of diagnosis might prove of little value until chance reveals the true nature of the condition Of the three men in the series two were allergic to plants (ragweed and poison ivy) This was easily ascertained by history and general examination It was not realized for a long time that the third was allergic to carbon paper One day however a waste basket containing carbon paper caught fire and he was enveloped in smoke Immediately a severe recurrence of the eruption of the eyelids developed Elimination of carbon paper and ink resulted in a cure Patch tests were negative

Eliminating three women from the series because of insufficient data Hazen found that of the remaining thirty women with ocular eczema twenty seven were suffering from contact allergy and three from seborrheic dermatitis Cosmetics accounted for eleven cases these included face powder two facial creams two perfume one nail polish four hair dye one hair wave one Drugs caused six cases of dermatitis Of interest were three cases due to fruit peel two to orange (Florida not California) one to apple one to primula and another to dog s hair The remainder of the cases were due to various chemicals such as soap powder hearth polish and insecticide spray He stated that still another case was due to the bite of a black fly (Simulium)

A much more detailed study of dermatitis of the eyelids was reported by

Kaalund Jorgensen of Copenhagen in 1951 (29) This author had encountered ninety six cases but reported only on eighty five because eleven were not examined sufficiently to be included in the analysis Twelve of the eighty five patients were men Seborrhea was the cause in three of these cases and occupational allergy in two Plants were responsible for three other cases as was a woolen sweater for still another Of the remainder one was due to pollen another to eye drops and the cause of the last was never determined The high incidence of dermatitis of the eyelids in women impelled this author to look for special reasons Interestingly enough the basic diathesis he has emphasized corresponds quite closely to what we have noted in regard to the incidence of staphylococcal eczema He found that the condition occurred mostly in women in or about the period of the menopause These patients have thin less elastic skin He thought that one of the reasons eyelid skin is particularly sensitive is because it has no sebaceous glands Although about half of his patients did exhibit varied degrees of dandruff the fact that thirty one other patients showed no evidence at all of seborrhea made him feel that this condition is not always the basis for the eczema The fact that most of the cases developed during the winter gave him the impression that the dry air of steam heat played a role in accentuating the essential dryness that he found to be so prevalent in these patients Kaalund Jorgensen noted that in thirty cases the eyelid alone were involved in the remaining forty three eczema was present elsewhere mostly about the face neck and ears

Perhaps because the women of Denmark seem to use fewer cosmetics than do those of the United States beauty preparations were responsible for the dermatitis in only twenty one of the seventy three women involved Kaalund Jorgensen found no instance of allergy to nail polish but noted that Danish women do not use it routinely On the other hand allergy to potted plants was very high totaling thirteen cases eight were due to primrose Six patients had allergy to the external use of drugs three to those used internally (one to quinine two to phenemal) Various household chemicals including turpentine and floor varnish accounted for seven cases Printer s ink caused two patients to have ocular eczema Eight patients had seborrheic eczema and one had psoriasis He attributed five other cases to mental factors Six he found to have obscure etiology In this latter group are included one patient who had an eruption whenever exposed to cold and wind and another who reacted to sunshine and heat

In regard to the importance of patch tests he found that in forty nine women so tested ninety five positive patch tests were elicited Some of these such as that to rubber he felt to be of little significance He also noted that several cases of cosmetic allergy proved entirely negative on patch tests Sensitivity to hair shampoos he considered very rare in Denmark It

should be remembered, however, that their use may not be comparable to that in the United States.

In contrast to the two reports quoted above, that of Swinney (30) of San Antonio, Texas, published in 1951, placed far less emphasis on the value of patch tests and much more reliance on both the history and the results of trial and-error observation—that is, the clearing of the lesions when the suspected substance is avoided, and their reappearance when it is reapplied. However, Swinney noted that in order to pursue this form of management patch tests should be done, even if the cause is known. If not visually convinced by patch tests the patient is reluctant to allow the trial and error approach. Of sixty three patients with periorbital dermatitis sixty-one were cured by removing the cause. In the other two, no positive cause was ever found. Eighty five per cent of the patients were women predominantly between the ages of 20 and 60. Swinney found that cosmetics were by far the most common cause of eczema of the eyelids, and that nail polish dermatitis was being encountered less frequently than hitherto. Of great importance in his series were cream-base shampoos. Although many patients reacted to patch tests with soaps, he believed that only where colored or perfumed soaps were used did ocular eczema occur. Two patients who were reactive to the red plastic frames of their eyeglasses, although negative to clear plastic, did not clear up till they had discarded their red frames. One woman who had ocular eczema due to lipstick had a negative contact test. The eczema did not clear up until she had left off her lipstick for ten days. When lipstick was reapplied, her periorbital dermatitis returned within three or four days on two subsequent occasions, but her lips did not become involved. In this series, occupational and plant sensitivities occurred in only three patients: a nut merchant sensitive to the oil of pecan, a file clerk sensitive to carbon paper, and a rancher sensitive to weed contactants. In his entire experience periorbital dermatitis of plant origin had occurred in only one instance.

Jacquet (31), reporting on what he called allergic blepharitis, noted such interesting causes as celluloid, nylon and automobile oil, as well as pilocarpine. Since four of his twelve cases were cured with Aureomycin it is possible that in some instances he was dealing with infectious eczematoid dermatitis, probably staphylococcal.

Kalb (32) found that periorbital dermatoses were due to perfumes, cosmetics, medicaments and shampoos. The frequency of periorbital eczema from ophthalmic drugs noted by Jirasek and Schwank (33) has been considered in the discussion of dermatoconjunctivitis.

Of twenty cases of allergy of the eyelids, El Mofty and El Gammal (34) found that contact allergy to drugs applied locally to the lids and conjunctiva accounted for eleven instances, cosmetics for five, physical al

lergy to sunlight for one, allergy to menthol cigarettes (after previous local application had caused allergy) for one The remaining two patients developed angioneurotic edema from drugs (phenolphthalein and argyrol) Interestingly enough the argyrol had been used topically in the conjunctiva but contact allergy did not occur Instead an immediate form of drug allergy resulted from systemic absorption

Sidi and Mawas (35) presented an excellent review of eczematous lesions of the eyelids in 1953 They emphasized the importance of contact eczema due to drugs cosmetics and industrial substances pointing out the frequency of allergy to chemicals with para amino groupings They stated that whereas in 1930 only one instance of sensitivity to paraphenylene diamine was encountered by 1952 ten per cent of patients were sensitive to the para group of substances Another point they made was the extreme frequency of allergy to antihistaminic creams especially Phenergan They reported allergy to artichokes occurring both in vegetable merchants and in housewives

These same authors (26) presented a most complete statistical study of the subject of ocular eczema in 1955 This appears to be the largest study available After eliminating from their statistics all cases of eyelid eczema associated with dermatologic conditions they had left three hundred and thirty nine cases of which only three hundred and twelve were the basis of the paper since twenty seven were not available for follow up In two hundred and fifty eight (82 7 per cent) of these three hundred and twelve cases patch tests were definitely positive Since in twelve of the remaining fifty four the cause of the allergy was proved by cure on elimination of the offending drug only forty two patients (13 5 per cent) were undiagnosed It is interesting in view of our work on the subject that Sidi and Mawas suggest that microbial allergy pneumoallergy and eczematous diathesis without external cause might be responsible in these cases Table 6 gives some idea of their general conclusions They felt that in round figures one might say that ophthalmic drugs caused about fifty per cent of eczemas while cosmetics were responsible for about thirty per cent The one hundred and thirty two patients with allergy from ophthalmic drugs have been mentioned in chapter 5 Among the occupational causes of interest were eight allergies in hospital workers (from antibiotics that they handled) two in beauticians (from giving permanent waves) two in furriers and one in a carpenter

A breakdown of the ninety two cases of cosmetic allergy was as follows nail polish twenty one eyelash paints twenty brilliantine nineteen hair dyeing twenty one beauty creams seven oil of ricin two vaseline for lids one rice powder one

Of special interest to ophthalmologists are the four miscellaneous cases

TABLE 6

Causes of ocular eczema (26)

Cause	Positive Tests	Per Cent of Total of Patients (312)	Per Cent of Total of Positive Tests (258)
Therapeutic			
Ophthalmic solutions	87	27 8	33 7
Ophthalmic ointments	45	14 4	17 4
Total	132	42 2	51 1
Cosmetics	92	29 4	35 6
Occupational	25	8 0	9 7
Plants (some occupational)	6	1 9	2 3
Miscellaneous	4	1 2	1 5

three were from plastic spectacle frames and one from a plastic prosthesis

Whereas in 1952 Sidi and Mawas had found ten per cent of patients sensitive to para compounds their new statistics indicated that about twenty five per cent of all the allergies they now encountered were due to these especially allergenic compounds These were the results of exposure to drugs cosmetics and industrial chemicals One antihistaminic alone—Phenergan—accounted for thirteen allergies or five per cent of proved cases

The varied experiences noted in the reports quoted indicate as noted above that statistics differ considerably since the specialty of the physician and the habits of his patients play a large role in the conclusions he draws

CLINICAL CHARACTERISTICS

It is quite apparent that contact dermatitis of the eyelids is much more prevalent in women than in men more because of frequent and repeated exposure to allergenic substances than because of any demonstrable endocrine factor There seems to be a definite tendency however to involve middle-aged women around the time of the menopause especially persons who show evidences of dryness of the skin or seborrhea and in our experience, indications of deficient thyroid metabolism While this diathesis might very well have a hormonal basis there is little evidence to support this In some women however the menstrual cycle appears to influence skin reactivity A hypothetic sensitivity to autogenous hormonal products has been suggested as the cause However the mechanism could be a triggering one increasing the already present hypersensitivity

Women are prone to develop allergic eczematous dermatitis of the eyelids from contact with cosmetics jewelry and articles of apparel such as a

new dress Cosmetic appliances, like eyebrow "tweezers (cilium forcep) and eyebrow curlers may also cause allergy Men generally react to chemical substances involved in either their occupations or their hobbies including oils soaps paints and sprays transmitted from the hands to the eyes However, the increasing use of colognes, deodorants and similar products by men probably will result in more allergy to cosmetics in men than has already been noted from shaving preparations and like products Moustache pomades and creams must be suspected because of the dyes and other chemicals they contain With both sexes hand to eye contact is the most common cause of the allergic reaction Both men and women appear apt to become allergic to plants, with men however, this is generally an occupational allergy *An individual can become allergic to products used* by another Husbands may be affected by wives cosmetics, wives may become allergic to their husbands' moustache cream Children likewise have developed contact sensitivities from products used by mothers Indeed observations are reported (36) where a parent s dandruff caused contact dermatitis of a child s cheeks and mouth Mention has already been made of a patient with paroxysmal asthma due to his wife's dandruff

Dermatitis

The dermatitis may be either unilateral or bilateral Often it starts as a minor wrinkling or inflammation involving the medial portion of the upper lid This change is usually the result of rubbing the eyes with fingers contaminated with the allergen The vulnerable and thin eyelid reacts readily due to ease of penetration and repeated exposure as discussed above This localization to the upper lid often aids in distinguishing cosmetic allergy especially that due to nail polish and hair preparations from drug allergy When allergy is due to a drug especially eye drops instilled in the lower cul de sac the earliest skin involvement may follow the usual paths of tear overflow—that is the canthi and the adjacent lower lid skin Sometimes however a streaklike pattern may result from the use of perfume or other fluid cosmetics Allergy to ointments often first shows changes along the lid margins which are swollen and inflamed but do not exhibit the scales and ulcers seen in typical blepharitis Certain patterns are diagnostic, such as allergy to the nickel or plastic of eyeglass frames where the dermatitis may outline the areas of contact of the face with the frames especially the sides of the nose and the temples or allergy to a hair net or bathing cap which is most intense on the forehead and eyebrow region (18)

Usually the conjunctiva is uninflamed, with no eosinophiles This is so because the conjunctiva is generally not exposed However conjunctival involvement has occurred in our experience in a patient with a long standing

allergy to a shampoo Presumably some of the offending substance entered the conjunctival sac while she was washing her hair Waldbott (18) mentions a patient who through daily use of a hair net developed an allergy which started on the forehead and gradually spread to involve the eyebrows eyelids, conjunctivae and corneae of both eyes, with marked visual impairment After several months the cause was recognized and elimination of the hair net resulted in complete recovery with full restoration of vision

The major symptom is itching This may be very severe The rubbing and scratching that usually occurs (often while the patient sleeps or does not realize it), serves to aggravate the condition by secondary infection or mechanical irritation The itching may precede the development of the eczema and again worsen as the lesions heal

As is readily understandable dermatitis about the eyelids especially in a woman will result in considerable anxiety nervousness and irritability It is important to remember that these symptoms are the result not the cause, of the eczema

Once allergy develops it generally persists for many years if not for life It is a mistake however to maintain that contact allergy is always permanent as many times the sensitivity tends to lessen or disappear entirely Previous lesions may flare up even if healed should another part of the skin come in contact with the sensitizing substance Waldbott tells of an ophthalmologist who had previously developed Pontocaine sensitivity in the fingers of the left hand Through the use of rubber gloves these areas had healed completely Eight months later however he applied a few drops of Pontocaine to his eye, using rubber gloves to protect his fingers Allergic dermatitis of the eyelid now occurred for the first time along with a recurrence of the dermatitis on the fingers Contact dermatitis may also change its pattern and character following the injection or the inhalation of antigens to which atopic sensitivity exists according to Waldbott According to him contact dermatitis may flare up during the hay fever season in the ragweed sensitive patient or, conversely clear if the hay fever is successfully treated by desensitization We have never observed this relationship and the general feeling as will be developed later is that the two forms of allergy are entirely distinct and unrelated

Diagnosis

History Careful history-taking is of the greatest importance in the diagnosis of contact allergy of the eyelids The use of leading questions is often valuable in opening avenues of thought otherwise dismissed by the patient as immaterial In a difficult case a contact diary in which the patient lists by name only all possible contactants encountered is very helpful The observations of the personal mannerisms and habits of the patient

during the interview sometimes afford worthwhile clues, as for exampl the constant rubbing of a ring or the straightening of stray strands of hair

Any possible relationship between the occurrence of the dermatiti and special contact with household articles cosmetics medicaments (especially locally applied), new garments pets the handling of foods plants and toys should all be explored The patient's occupation in all its ramifications must be carefully considered Wolf (37) tells of ocular eczema due to nickel allergy occurring in the proprietress of a small candy store this resulted from the constant handling of many coins of low denomination (pennies and nickels) Hobbies are of particular interest Allergic eczema of the eyelids has occurred in our experience from the cleansing fluid of coin collectors the glue of stamp lovers the painting materials of those who find relaxation in the use of water colors and oils, the chemicals of the amateur photographer and all the contactants encountered when engaged in sports including the equipment itself Since plants food clothing and sports vary at different times of the year the seasonal occurrence of allergies highlights these factors One patient developed eczema of the eye lids only when she took her moth preserved clothes out of storage in the fall Similarly pin pointing the reaction to specific days such as wash days suggests laundering materials such as soapless detergents the occurrence before holidays might incriminate the beauty parlor or the barber shop as the source of the allergy Mention has already been made of the fact that the offending allergen instead of being something the patient him self has used may be a substance used by another person with whom the patient is in intimate contact such as a husband or wife Similarly poison ivy dermatitis may be contracted from a dog who has been directly in contact with the plant even though the patient has not been near it

Patch tests Since the site of eczematous (contact type) allergic dermatitis appears to be strictly epidermal not deeper in the skin patch tests are useful in proving contact allergy Immediate wheal testing by intradermal injection useful in other types of allergy is not a correct diagnostic procedure here Even the most superficial intracutaneous or scratch test carries the allergen through the epidermis into the cutis

An apparent exception to this has been mentioned in chapter 5 Intolerance to mixtures containing neomycin was proved (in one series) to be the result of allergy to this antibiotic despite negative patch tests on the basis of positive delayed (tuberculin type) reactions after intradermal injections of neomycin A dermal rather than epidermal site of sensitivity was postulated

A patch test is carried out by applying a small amount of the suspected substance to a site of normal skin of the patient and covering it with an innocuous impermeable material which is sealed to the skin with adhesive

and left in site for from one to four days Sometimes one must read the reactions for as long as five days after the patch is removed as the test may only then become positive Usually contact for twenty four hours is enough The true allergic reaction increases (as a rule) in intensity for twenty-four to forty-eight hours after the patch is removed For testing liquids a piece of gauze one fourth inch square is saturated Powders are placed on moistened gauze For solids insoluble in water make a saturated solution in a solvent wet some gauze with the solution but let the gauze dry first before applying it to the skin to eliminate the action of the solvent For ointments the same procedure as for liquids is used

A negative patch test does not necessarily rule out the test substance as a causative agent because 1) under the test circumstances the actual mechanism producing the inflammation may be lacking (like a photo sensitive chemical which requires exposure to sunlight and will not give a positive reaction under other conditions) 2) the patient may no longer be sensitive 3) the actual sensitizer is not applied 4) a local sensitivity only, is present and the site of skin tested is not sensitive (for a positive result in such cases the patch test must be applied at the original site of the dermatitis), and 5) occasionally certain predisposing factors such as heat friction and maceration of the skin are required for a positive result It is possible that where such maceration is necessary a dermal sensitivity is operative and that intradermal tests may prove positive as noted above with neomycin

A positive patch test on the other hand may not be diagnostic if the test material is used in too concentrated a form as then it may act as a primary skin irritant Physical irritation with actual scratching of the skin from hard objects may give a false-positive reaction when certain substances are tested Furthermore once contact allergy occurs many other substances will cause positive contact reactions in a given individual even though they are not responsible for the original dermatitis

The dangers of patch testing in extremely sensitive individuals should not be minimized Certain persons are so sensitive that any prolonged exposure to the contactant may result in extremely severe inflammation and secondary infection One such case in our experience necessitated systemic sulfonamide therapy for about a week because of such an occurrence In this instance the patient removed the patch several hours after it was applied because itching became so severe yet sensitivity devel[illegible] in very high degree despite this short period of contact It is [illegible] idea in such highly sensitive patients to observe them in the of[illegible] half an hour after the application of the patch and look at it [illegible] fore allowing them to leave Indiscriminate patch testing [illegible] contact allergies hitherto not present This can be minimized [illegible]

extent by avoiding agents which are known to sensitize the skin easily, and also by not allowing the patch to remain on the skin any longer than is absolutely necessary, preferably not more than two to three days.

IMPORTANT ALLERGENS CAUSING OCULAR ECZEMA

At this point it may be useful to consider the special properties of some of the more important causes of allergic eczema of the eyelids.

Ophthalmic Medicaments

These have been considered at length in the discussion of allergic dermatoconjunctivitis and need not be reviewed again. Most instances of this form of allergy begin in the conjunctiva, as it generally is the focal *point of contact of the drug. However, medicaments directly* applied to the eyelids do not cause conjunctivitis and might be mentioned here. Antiseptics such as iodine, picric acid, mercurials, Zephiran and other quaternaries used for preoperative surgical preparation are common offenders. Substances used for wet dressings, such as boric acid and witch hazel (fig 53), may cause similar allergies without involving the conjunctiva to any great extent. Most of the time, however, ointments, especially ones used to relieve itching or irritation of the eyelids, such as those containing anesthetics, antihistaminics or even corticosteroid, are the prime offenders. Even the mild ointment bases *themselves may*



Fig 53 Contact allergy to witch hazel applied to eyelid. The conjunctiva was uninvolved.



Fig 54 Contact allergy to skin lotion containing an antihistamine with a para chemical linkage Patient was extremely sensitive to paraphenylenediamine on patch test (courtesy of New York Skin & Cancer Unit)

cause the reaction Special emphasis must be placed on the allergic propensities of antihistaminic lotions (fig 54) or ointments especially Phenergan So much contact allergy has resulted from these ointments that they are no longer accepted by the Council on Pharmacy and Chemistry of the American Medical Association Spectacles (see below) also cause eyelid allergies as may solutions used to clean lenses

Adhesive tapes Reactions to adhesive tapes are basically of two types 1) a traumatic variety secondary to mechanical factors such as maceration friction and tension, and 2) contact allergy to various ingredients in the tape (fig 55) The traumatic reactions are of short duration the allergic ones last for a number of days In addition a rare form of primary irritation due to the incorporation of irritant substances in the adhesive may also occur

The most common causes of allergy are the resins or their major constituents (rosin Burgundy pitch and abietic acid) and the rubber used in the adhesive although positive reactions to many other ingredients have been demonstrated on occasion In line with this Keil (38) has shown that the etiologic basis often varies and is sometimes multiple The rosins used are of two main types gum rosin derived from turpentine and wood rosin Where allergy to adhesive tape containing gum rosin occurs (mainly European products) sensitivity to turpentine often is present Wild South American Bent Para rubber smoke cured over nuts of the Urucuri palm has frequently been responsible for the reaction



Fig 55 Contact allergy to adhesive tape (courtesy of Cl y Adms Co)

This type of rubber contains many impurities In recent years manufacturers have made considerable efforts to eliminate such possible causes although the introduction of plastic adhesives has resulted in a new source of allergy One type of adhesive has sodium propionate and sodium caprylate incorporated in it on the premise that the antifungal and antibacterial properties of these agents minimize the likelihood of allergies to adhesive compounds As has been established (39) sodium propionate is a relatively hypoallergenic drug

Of particular interest to the ophthalmologist are allergic reactions to *transparent tapes such as Scotch tape since he uses this form of adhesive* material so extensively for all eye dressings As far as the skin of the face and forehead is concerned Scotch tape appears to be definitely less allergenic than ordinary adhesive tape It may often be used safely in patients who have proved allergic to adhesive tape Allergies do occur however Keil (40) who reported the first such allergic *dermatitis* occurring in a patient known to be sensitive to adhesive tape decided after careful etiologic investigation that an ester gum (glycerinated wood rosin) was responsible in his case Benkwith (41) also reported allergy to Scotch tape in a patient sensitive to another transparent adhesive tape as well as to zinc oxide adhesive He felt that the allergy occurred from the rubber but did not actually demonstrate this

We have encountered instances of allergy to both Scotch tape and ordinary adhesive where other special adhesive products (such as Elastoplast) were harmless However all adhesive materials cause allergies on occasion

Cosmetics

In a broad sense a cosmetic may be considered as any article or component of such article used on any part of the human body to cleanse beautify promote attractiveness or alter the appearance While this definition includes substances used internally for such purposes in practice such usage is essentially external

History. Although the first authentic records concerning cosmetics are to be found in early Egyptian papyri still earlier evidence indicates the extent to which beauty aids in crude forms have been utilized from earliest time It is likely that cosmetics had their origin in the East but there are neither written evidences nor cosmetic receptacles (often a clue to such practices) still extant to prove this It is known that cosmetics were used by the ancient Sumerians in Mesopotamia at the time the first known written language evolved almost five thousand years ago However it seems that the Egyptians were the first to completely develop the practice into a fine art They passed on the custom to the Hebrews then to the Greeks and finally to the Romans During the reign of Cleopatra the use of cosmetics especially in regard to the embellishment of the eyes seems to have reached a peak never again achieved All in all it appears that women of ancient times expended more time and went to far greater extremes to beautify themselves than do modern women They hesitated at nothing and submitted to many long and torturous proceedings often using most nauseating and repulsive concoctions (42)

The use of cosmetics then spread rapidly throughout Europe reaching such extravagant proportions in England that in 1770 the following bill was introduced in Parliament to protect men from being beguiled into matrimony by the use of artificial adornments (43) That all women whatever age rank profession or degree whether virgins maids or widows that shall from and after such Act impose upon seduce and betray into matrimony any of his Majesty s subjects by the scents paints cosmetic washes artificial teeth false hair Spanish wool iron stays hoops high heeled shoes bolstered hips shall incur the penalty of the law in force against witchcraft and like misdemeanors and that the marriage upon conviction shall stand null and void This law like a previous one passed during the regime of Cromwell in 1650 met the usual fate of unpopular statute It was first completely ignored and then forgotten

In the United States the history of the use of cosmetics parallels that of Europe (44) The aboriginal Indians had considerable knowledge of dyes and pigments, which they used in body painting Iron salts were used with vegetable extracts In colonial times the use and tolerance of cosmetics varied as much as Puritan New England differed from Cavalier Virginia However, even relatively moderate Quaker Pennsylvania included in her statutes the act of 1770 quoted above whereby marriage could be annulled on the basis of deception through the use of cosmetics

Diagnosis. In the diagnosis of eczema of the eyelids due to cosmetic it must be remembered as explained above, that only the eyelids may react, even if the allergenic substance was applied at a place remote from them Often the skin of the medial portion of the upper eyelid is involved This is so typical of early mild allergy of the eyelids that it deserves special emphasis Generally new and previously untried cosmetics are the offenders However, even if a cosmetic has been previously used without reaction for many years it should not be entirely exonerated because the manufacturer may now have changed the formula or the method of production in some way Even if he has not impurities introduced into one special lot of the manufactured product may be responsible Moreover too frequent or too vigorous use, possibly on an irritated skin may cause allergy in instances where more judicious application is harmless Nowadays, most allergies due to cosmetics are the result of the perfumes used and of impurities in manufacture as the most flagrant offenders have been eliminated Deterioration due to age or improper storage may change a safe cosmetic into an irritant or a sensitizer Sometimes the cosmetic itself is innocent, but liners in bottle caps or contamination of containers may cause allergy Similarly, allergy may occur from utensil used for application, such as a powder puff or other contents of a makeup kit

Sometimes the application of face powders or face creams in themselves not allergenic to the individual involved may result in allergies because of contamination with traces of fingernail polish which may have chipped off and mixed with the cream or powder Similarly, deodorants may become contaminated with dyes from dresses or other goods through finger contact

As explained previously uncovered application of a cosmetic is preferable to a patch test Moreover, cosmetics containing photosensitizing materials such as lipsticks should be tested on exposed areas of skin In diagnostic testing for cosmetic sensitivity, instead of doing a patch test it is better to apply the cosmetic daily in the way it is generally used because in normal use the uncovered cosmetic loses much of its substances by evaporation (16) Covering the cosmetic by a patch test does not

permit this evaporation and thus may give false positive reactions with cosmetics that are actually harmless when used in the ordinary manner

A recent study by Kramer (45) sheds light on both the relative frequency of the various types of cosmetic allergy encountered in general (not specifically eyelid allergy) and the relative importance of various cosmetics to the users In four hundred and fifteen cases reported to her lip sticks accounted for about one half of the allergies Unfortunately no data were included concerning hair dyes and cold waves which are frequent offenders *With these limitations understood her studies show the* following statistical incidence of cosmetic allergy lipstick forty eight per cent creams and lotions nineteen per cent nail lacquer fifteen per cent face and body powders four per cent soap and soap products four per cent miscellaneous six per cent unidentified cosmetic reactions four per cent

Certain types of cosmetics are of special importance in the production of contact allergy of the eyelids These are discussed below

Nail polish and nail lacquer Allergy to nail polish (fig 56) and nail lacquer is one of the most important and possibly still the most frequent of all the ocular allergies due to cosmetics Dermatitis involved the eyelids in seventy eight of one hundred cases of all types of nail polish sensitivity in one reported series (46) The offending ingredients are believed to be the synthetic resins such as methacrylates and possibly



Fig 56 Contact allergy to nail polish (N Y and Mass Clin Ophth 195)

the dyes used Methacrylates are nowadays being increasingly utilized as artificial elongators for broken and bitten nails and allergies from such usage have been encountered Nail polish removers (oils dissolved in ethyl acetate) may be sensitizers The characteristic areas involved in nail polish allergy besides the eyelids (especially the upper lid) include the sides and back of the neck and the ears—externally as well as inside the canal

Face powders Face powders used to be sensitizers because of the orris root and the rice powder content (fig 57) These ingredients are rarely used at present having been replaced by titanium salts Now any allergy to face powder is usually traced to perfumes and to impurities in manufacture and packaging

Creams The creams most commonly causing allergy are bleaching creams freckle creams vanishing creams and cleansing creams Emollient creams are less apt to do so Reactions to bleaching creams generally are due to monobenzyl ether of hydroquinone or to mercurial salts in freckle cream mercurial salts and salicylic acid may be the source In cold cream (fig 58) and vanishing creams in general the major offenders are perfumes detergents lanolin cocoa butter almond oil or any other oil phase ingredient or emulsifying agent Astringent creams used to close pores may contain resorcinol which is a sensitizer We have encountered



Fig 57 Contact allergy to face powder containing rice (Courtesy of Dr E Mawa)



Fig 58 Contact allergy to cold cream



Fig 59 Contact allergy to hormone cream

eyelid allergy to hormone cream (fig 59) supposedly a rare occurrence Hand creams and lotions may similarly cause allergy sometimes limited to the eyelids Even hypoallergenic creams (fig 60) may cause allergy

Rouge Rouge appears to be an infrequent cause of contact allergy of the eyelids Ereaux (47) has observed an interesting instance of such an occurrence as often happens it was finally diagnosed by the patient herself

Lipstick Lipstick dermatitis is usually due to the indelible dyes such as bromfluorescein and the eosin group or possibly to the minute amount



FIG 60 Contact allergy to hypoallergenic cream used to cover blemish on nose Eyelid dermatitis occurred due to indirect contact

of perfume used Schwartz and Peck (17) feel that the fluorescent dyes are important factors in the reactions they cause They have seen cheilitis occur in clowns exposed to bright summer sunlight In thirty two consecutive cases of lipstick cheilitis reported in one series (48) the eyelids were involved in three patients When the indelible dyes were eliminated from the lipsticks the eyelid eczema cleared The present general tendency of manufacturers to market high staining indelible type lipsticks may result in an increase of allergies

Perfumes The importance of perfumes as a major cause of cosmetic allergy is readily appreciated once one realizes how complicated perfumes may be and how much they are used Not only are perfumes applied directly but almost all cosmetic products and sometimes even medicaments contain perfumes to make them more attractive Such perfumes often sensitize

Modern perfumes are blends of many odorous chemicals of both natural and synthetic origin (49) Their production is involved and specialized often utilizing a large number of ingredients Thus to determine the specific cause when allergy to a known brand of perfume has occurred is a herculean accomplishment even if the details of the entire manufacturing process are made available (which is not always the case) Table 7 lists ingredients of perfumes reported to have been responsible for contact dermatitis Of special interest is oil of bergamot which because

TABLE 7

Sensitizing ingredients of cosmetics

Perfumes	
Almond oil	Jonquil oil
Angelica oil	Lavender oil
Arnica flowers	Lemon oil
Balm of Gilead	Lime oil
Balsam of Peru	Limonene
Bay oil	Linalool
Benzaldehyde	Mandarine orange oil
Benzyl benzoate	Methyl heptine carbonate
Bergamot oil	Methyl naphthyl ketone
Betanaphthol	Methyl nonyl acetaldehyde
Canada balsam	Neroli oil
Cassia oil	Olibanum gum
Cinnamic aldehyde	Orange oil
Citral	Origanum oil
Clove oil	Orris oil
Coriander oil	Peppermint oil
Diethyl phthalate	Spearmint oil
Eucalyptus oil	Terpenes
Eugenol	Terpineol
Geranium rose oil	Tuberose oil
Heliotropin	Vanilla beans
Hyacinth oil	Ylang ylang oil
Jasmine oil	
Creams	
Ammoniated mercury	Ethanolamines
Beeswax	Lanolin
Benzoyl peroxide	Salicylic Acid
Borax	
Hair preparations	
Amidol—(dye)	p-Phenylenediamine (hair dye)
Bayberry oil—(lotions)	p-Aminophenol (hair dye)
Bay laurel—(lotions)	p-Toluenediamine (hair dye)
Cantharidin—(lotions)	m-Toluenediamine (hair dye)
Carbolic acid (phenol)	Pyrogallic acid (hair dye)
Ethanolamines—(hair wave solutions)	Phenol formaldehyde resins
Karaya gum	Resorcinol
Lanolin	Salicylic acid
Methacrylate resins (in lacquers)	Sodium persulfate (hair wave sets)
Morpholine—(hair wave sets)	Betanaphthol
Orris root—(dry shampoo)	
Lipsticks	
Bromo acid	Eosin dyes
Castor oil	Bromfluorescein
Lanolin	

TABLE 7—*continued*

Nail polish	
Alkyd resins	Methacrylate resins
Ethyl acetate	
Miscellaneous	
Acacia (lotions)	Quinine salts (sunburn lotion)
Aluminum salts (antiperspirant)	Rice powder (face)
Coconut oil (soap)	Rosin (adhesives)
Formaldehyde (antiperspirant)	Wheat starch (powder)
Methenamine (deodorant)	Zinc formate (antiperspirant)
Phenol (for face lifting)	
Antiseptics and preservatives used in cosmetic preparations	
Amyl metacresol	Eugenol
Benzoic acid	Orthophenylphenol
Benzoin gum	Phenol
Boric acid	Phenyl mercuric salts
Carvacrol	Potassium sulfide and sulfite
Chlorothymol	Resorcinol
Cresol	Thymol

of its photosensitizing nature may result in skin reactions long after the perfume containing it has been used

Suntan preparations Possibly the reason that suntan preparations which contain potentially sensitizing ingredients have not been reported as causing allergies is that any dermatitis from such products is attributed to or considered to be a sunburn (17)

Deodorants and antiperspirants Although dermatitis from these products is usually limited to the axillae since they are often applied manually other areas, such as the eyelids may be involved Allergy may result from use of either the liquid (including sprays) or the cream types *Hexamethylenetetramine (liberating formaldehyde)* aluminum salts methenamine and zinc formate may be the sensitizing agents

Depilatories Depilatories are brought to the eyelid region only through secondary contact They are essentially primary irritants but may give rise to allergic reactions

Soaps Reactions to soaps are more often the result of primary irritation than of allergy because of the alkalinity and emulsifying action of the soaps When allergies do occur these are, again usually due to incorporated perfumes However allergies to fillers, fats fatty acids and other ingredients such as medicaments antiseptics or dyes are sometimes demonstrable

After shave lotions Allergy to these is usually due to the perfumes

used In one instance, however, quinine was the allergen Irritation from the alcohol used must be differentiated

Tooth paste Dyes or preservatives in dentifrices as well as other *ingredients may on extremely rare occasions result in allergy of the* eyelids In one report (47), the responsible agent was erythro ine Peri ocular and circumoral dermatitis occurred

Hair and eyelash dyes Of the greatest importance to ophthalmologists are those substances used for the purpose of dyeing hair especially that *of the eyebrows and eyelashes Certain types of dyes such as oxidation* coal tar chemicals like paraphenylenediamine are potentially so toxic and allergenic that the most serious ocular accidents may follow their local use resulting at times in blindness and on occasion even death It is thus necessary for the ophthalmologist to have some knowledge of the *subject*

Coloring the eyelids brows and lashes as well as the hair dates back to the earliest times In the Bible Ezekiel (23 40) reproaches Hebrew women for such practices and Jezebel s painted eyes (II Kings 9 30) are well known Vegetable dyes such as henna appear to be the earliest known hair dyes *and were used by the ancient Egyptians as well as by* King Solomon s wife Henna was and still is also used for dyeing finger nails palms and soles of feet as well as the manes and tails of horses Metallic dyes such as lead salts appear to have almost as old a history The Chinese are believed to have been among the first to employ them as coloring *agents The Egyptians also used metallic pigments for this* purpose especially kohl

Kohl This preparation is believed to have originated in Egypt However, its use to blacken the eyelids eyelashes and eyebrows has been popular for thousands of years especially in the East Our own studies indicate that *contrary to general belief the actual ingredients of the* product varied so that the term kohl must be considered generic rather than of fixed composition or formula In fact although generally attributed to Arabic derivation (kuhl) the word kohol in Hebrew means to dye blue Most of the time antimony or lead was used in the ancient recipes sometimes black oxide of manganese or carbon black was substituted The variety introduced into Europe several centuries ago contained India ink (43) Several types of kohl or Sumar are still manufactured in Pakistan one contains black oxide of manganese the other carbon derived from burning organic material

Bleaching agents are likewise of considerable antiquity The great admiration of the Romans for the blond hair of their captives from northern countries led them to utilize many of their native minerals such as rock alum quicklime crude soda and wood ash for this purpose (50)

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Metallic dyes. The metallic salts used as dyes may cause both toxic and allergic reactions. Many of these salts are used in conjunction with pyrogallol, itself a potent sensitizer, or with sulfur. Pyrogallic acid hastens the actions of the metallic salts and may render them more harmful as irritants and allergenic agents. The metallic salts appear to act by plating the outside of the hair by means of the deposition of an insoluble oxide or sulfide. The use of metallic dyes by women has decreased greatly because these substances are incompatible with permanent waving and oxidation coal tar dyes. Because of this they are nowadays rarely applied in beauty parlors; instead their major sale is for home use, especially as gradual hair darkeners or "restorers" for men.

While there generally is little danger of toxic absorption of these chemicals when used as hair dyes, if the skin is broken such absorption may become hazardous. When used as moustache dyes, however, toxic reactions may occur through the mucous membrane. Lead, silver and copper hair dyes, the ones most commonly used in the United States, have occasionally been known to cause allergic dermatitis. Silver has caused allergic dermatoconjunctivitis. Cadmium, cobalt, antimony and nickel also give allergic reactions. Tin, aluminum, bismuth and iron appear to be relatively innocuous. The use of manganese as a hair dye is obsolete. It is questionable whether argyria has actually ever occurred following the use of silver hair dyes (50).

Synthetic organic dyes. Actually the first organic hair dye to be synthesized was pyrogallol, which has been used now for about one hundred years, either alone as a progressive dye or as an adjuvant for vegetable and metallic dyes. Its allergenic propensities have been mentioned under those headings. An instance of allergic dermatoconjunctivitis and dermatitis of the forehead and scalp resulting from its use in combination with hydrogen peroxide was reported by Renedo (53).

The introduction of paraphenylenediamine and other oxidation coal tar dyes in the 1880's marked a great technical advance in the dyeing of furs, feathers and human hair. Their ease of application, the natural appearance they impart to the hair and their compatibility with permanent waving (introduced later) are advantages recognized both then and today. Thus at the present time, despite legal restrictions in a number of countries and certain safeguards in the United States of America, para-

All these natural dyes and bleaches are not without their occasional toxic (poisonous), irritant, and allergic effects. With the introduction of coal-tar products, however (only about 75 years ago), a relatively minor problem became a much more serious one, not only because of the dangers inherent in these chemicals themselves but because the technical advantages they offered made their use so popular.

In a broad sense five groups of hair coloring agents are available at the present time: 1) bleaching agents, 2) temporary coloring, 3) natural organic (vegetable) dyes, 4) inorganic (metallic) dyes, and 5) synthetic organic dyes. The first two types are relatively unimportant as sensitizers; the others, especially the synthetic dyes, are much more important. Modern bleaches cause dermatitis rarely, if at all. Hydrogen peroxide is used in combination with ammonia for this purpose or else utilized alone in rinse. For the "platinum blond" effect a rinse with dilute solutions of methyl violet or methylene blue is then applied. Temporary colorings with powders and crayons are not used enough to be of clinical importance. Temporary color rinses, of themselves relatively harmless, are often combined with detergent surface active agents such as sodium lauryl sulfate and alkylated aryl sulfonates. These may be the basis for allergic as well as irritative reactions. The same observations apply to temporary color shampoos.

Dye removing is occasionally a difficult and dangerous procedure that requires the expert use of strong chemical agents which may act as primary irritants.

Organic (vegetable) dyes. These are natural dyes obtained from plants and woods and appear to be the least harmful of the major dye groups. The most important of the vegetable dyes is henna (Lawsonia); other plant dyes include indigo and camomile, used in combination with henna. Of the many wood extracts originally in use only Brazilwood, catechu, walnut and nutgalls (a source of pyrogallol) are of any importance. Although henna does combine with the keratin of the hair, vegetable dyes in general only coat it. Thus they are not long lasting. The unnatural appearance and brittle character of the hair resulting from the application of vegetable dyes are other drawbacks to their use.

Deleterious reactions from pure vegetable dyes appear to occur exceptionally, if at all. However, since they are rarely used in their pure forms but instead are sold in combinations with many other products, they may be unjustifiably blamed for allergic reactions. Many so-called "henna" compounds contain little or no henna, or may contain sensitizing aniline chemical. Bab (51) originally reported six instances of allergic reactions after dyeing the eyelashes with henna preparations. Conjunctivitis was noted in all cases; in two of the patients keratitis and corneal ulcers also occurred. Later (52) he observed five more cases of such allergy but by

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phenylenediamine is by far the commonest compound used for the dyeing of hair

Oxidation coal tar dyes are more properly called dye intermediates since in the original state they cannot color the hair To act as dyes these compounds must undergo oxidation The fundamental technique of the process is to apply a one to three per cent solution of the dye in a freshly prepared mixture with the developer or oxidizing solution hydrogen peroxide With a one per cent concentration blond hair is produced, two per cent brown three per cent, black

Paraphenylenediamine itself is believed to be relatively harmless The actual sensitizer appears to be its first intermediate oxidation product quinone diimine which is unstable Continuance of the oxidation process finally results in Bandrowski base, which is harmless Thus it is important in dyeing hair to be sure that enough oxidizer is used so that oxidation of the paraphenylenediamine is complete Other members of the oxidation coal tar group of dyes, such as paratoluylenediamine not restricted in Europe were originally erroneously believed to be less toxic and are less effective

Actually modern hair dyeing practice is more complex including the use of modifiers such as pyrocatechol resorcinol and pyrogallol antioxidants such as sodium sulfite alkalizers like ammonium hydroxide and developers like hydrogen peroxide or solid urea peroxide Many of these chemicals are of themselves allergenic in character

In addition to the classical clear liquid form of supplying oxidation dyes they may be merchandised as shampoos tints color shampoos cream dye bleach dye combinations powder in capsules and as soaps These products are mentioned as a warning that unsuspecting individuals may be exposed to them through accident or carelessness with possible allergenic sequelae

Reactions from paraphenylenediamine and related oxidation coal tar dyes Oxidation coal tar dyes are toxic irritating and sensitizing Systemic reactions from local application have caused death The effects resemble those of histamine Ocular manifestations of such poisonings (which are rare) include diplopia lacrimation chemosis exophthalmos and optic neuritis (54–56) Oral or subcutaneous administration of paraphenylenediamine in the experimental animal is followed by intense watery edema of the entire head (57)

Most reactions from locally applied coal tar dyes are of the allergic (fig 61) or irritant varieties The danger of serious sequelae of this type is especially great when these dyes are used about the eyes and orbital region Such usage is now prohibited in many countries

The actual percentage of incidence of allergy to paraphenylenediamine



Fig 61 Contact allergy limited to the eyelids due to secondary contact from hair dye containing paraphenylenediamine (Courtesy of New York Skin & Cancer Unit)

is a matter of some dispute. Ingram (58) found in 1932 that four per cent of the population gave positive responses, which might appear anywhere from twenty-four hours to twenty-four days after application. In contrast to this extremely high figure, Schwartz and Barban (59) found in 1952 that no reactions were elicited in over one thousand patients whom they tested and that the incidence of reactions from actual use of coal-tar hair products was only 1:80,000. This seems to us to be rather low and to be contrary to the experience of many other investigators (57). Schwartz and Barban believed that impure paraphenylenediamine—originally used and now, according to them, eliminated—was the cause of the previously higher incidence of allergy. The phenomenon of cross sensitization discussed earlier in this chapter, especially in regard to the frequency of allergy to aniline ring products with para-linkages, may also play a role in allergies to paraphenylenediamine. Thus cross sensitization with local anesthetics has been noted. In patients with contact allergy to paraphenylenediamine, Baer and Leider (60) have observed exacerbations on feeding them certified related azo dyes. Of special interest to ophthalmologists was the case reported by Rothman in discussion of this paper. A patient with contact eczema of the eyelids due to the yellow color added to Florida

oranges was entirely free from symptoms for over a year after avoiding such oranges A relapse then occurred which was traced to Nembutal the capsule of which is dyed with the same group of accepted yellow azo dyes

Certain cosmetic chemists feel that the danger of the use of coal tar chemicals as hair dyes has been greatly exaggerated and that if proper precautions such as preliminary skin testing twenty four hours before use is practiced these compounds are not especially dangerous (50) The many millions of uneventful applications of the amino dyes are cited as evidence to support this contention These precautions are now required by law in many countries However, the question arises whether such safeguards are truly adequate as serious reactions after testing need not occur within the usual twenty-four hour period of observation the law requires but instead may occur later Moreover, many users do not appreciate that allergy may first occur only after many applications and thus often neglect to perform repeat skin tests in persons who have previously utilized the product without harm

Local ocular reactions One cannot overemphasize the possible hazards from the use of coal tar products as eyebrow and eyelash dyes (fig 62) Both blindness and death have occurred from such usage which is now generally outlawed

Although local eye changes including coloration of the cornea and con



Fig 62 Contact allergy from eyelash dye containing paraphenylenediamine (S J A Mawas Clin Ophth 1952)

junctiva had been noted from aniline dyes as early as 1876 (54) the great dangers of these products when used in the orbital region were first dramatically brought to the attention of everyone by a series of unfortunate experiences recorded mainly in the *Journal of the American Medical Association* in 1933 and 1934 Most of the reactions were due to Lash lure a product that did not contain paraphenylenediamine but instead consisted of a related aniline derivative (probably paratoluylenediamine) and large quantities of magnesium (61) others resulted from Larieuse which did contain paraphenylenediamine The least serious reactions from Lash lure consisted of severe dermatoconjunctivitis (61 62) Removal of the eyelashes proved to be very important in controlling the reactions Other reports (63 64) however noted corneal involvement with central corneal ulcers which in some instances were complicated by uveitis and secondary glaucoma Necrosis and sloughing of the cornea occurred Blindness resulted in several patients Hordeola and furunculosis were frequent It might be observed parenthetically that the allergic reaction while certainly the precipitating cause may not have been the only reason for these terrible sequelae As often regrettably happens in practice once corneal damage occurs secondary infection from contaminated medicaments supervenes Nowadays due to legal requirements concerning sterility this is less apt to happen but unfortunately it still does

Forbes and Blake (65) reported an instance of death following the use of Lash lure The patient as fate would have it was having her brows and lashes dyed by her daughter a beautician Such severe burning occurred immediately after application of the dye to the eyebrow and the eyelashes of the right eye after preliminary plucking that the left eye was not treated Within two hours the lids were so swollen that the right eye could not be opened and the patient became violently ill with a fever of 104°F Eight days later when the authors first saw her a sloughing ulcer of the right eyelid was present the conjunctiva was ulcerated and secondarily infected with *Staphylococcus aureus* and the cornea was hazy The patient died that night It was felt that plucking the hairs provided multiple portals of entry resulting in this violent local and systemic allergic response We ourselves wonder if a toxic as well as an allergic reaction occurred in this case

Reactions from Larieuse containing paraphenylenediamine have ranged from severe dermatoconjunctivitis (66–68) to bilateral necrosis of the cornea (69) In the latter instance hypopyon and perforation occurred in one eye in the other eye ultimate vision was only 10 100 following corneal ulceration and operation for secondary glaucoma Skin test with paraphenylenediamine was four plus Preliminary patch testing would have saved this patient's eyes

Other instances of reactions from eyelash dyeing with coal tar products have been reported (70-76). One interesting case (77) had had dermatitis from rabbit fur dyed with paraphenylenediamine. Four years later the patient developed conjunctivitis from an eyelash dye.

Treatment of reactions from coal tar dyes. In the treatment of contact reactions from amino dyes the first consideration must be the getting rid of whatever remaining paraphenylenediamine is present. To this end it may be necessary to cut off the hair or even shave the scalp in severe cases. Generally, however, thorough shampooing and rinsing with hydrogen peroxide suffices. In reactions after use on the eyebrows or lids the cilia should certainly be cut off and the eyebrow hair shaved if the reaction warrants it. To block toxic phenomena ACTH and steroids should be used in adequate parenteral and topical doses in all patients.

Governmental regulations regarding hair, eyebrow and eyelash dyes. The specific use of paraphenylenediamine (but not others of the group) was first restricted in Germany, and the product listed as a poison in 1906 (50). Similar restrictions have obtained in France since 1911. Legal limitations but not prohibitions regarding paraphenylenediamine exist in a number of other countries. In the United States a more flexible yet more inclusive regulation is in force. The Federal Food, Drug and Cosmetic Act permits the use of all coal tar hair dyes if these products have a specific caution label attached requiring that preliminary patch testing be done. However, the use of all coal tar hair dyes for coloring the eyebrows and eyelashes is expressly prohibited. Most states in this country have similar safeguards.

The Sanitary Code of the City of New York includes further restrictions in regard to hair dyes. Preliminary patch testing twenty-four hours before use is mandatory for amino dyes. If any reaction results from the test they are prohibited. Metallic compounds must have caution labels. No hair dye of any type is permitted if the scalp or adjacent area shows evidence of abrasion, eruption or other diseased condition. No hair dye containing any coal tar color or intermediate or a metallic compound and no cosmetic containing a coal tar color may be used on the eyebrows, eyelashes or anywhere in the orbital area. However, compounds containing less than five per cent silver nitrate are permitted. Antimony, arsenic, cadmium, chromium, mercury (except ammoniated mercury up to five per cent), lead (except in hair dyes), selenium and thallium may not be used in any cosmetic compound.

Mascara. Mascaras generally consist of an oil soluble soap base, usually triethanolamine stearate or oleate, combined with such materials as carnauba wax or beeswax, or into which color pigments such as carbon black, bone black, oil black, methylene blue, ultramarine blue, iron oxide browns



Fig 63 Contact allergy to mascara

(burnt sienna) iron oxide yellows (ochres) or a combination of these have been ground The use of triethanolamine salts results in less alkaline and therefore less irritating mascaras than those with simple soap bases Mascara is available in cake cream and liquid forms Allergy to mascara (fig 63) is rather uncommon and usually is due to the base used since the dyes employed are rarely sensitizers

Eye shadow Cream eyeshadows the most popular types now in use contain blue green and violet pigments or combinations of these colors in an ointment base consisting mainly of petrolatum and some lanolin ceresin beeswax or spermaceti The usual coloring agents are carbon black iron and chromium oxide pigments but no free chromium and carmine (cochineal from dried insects) mixed with titanium dioxide or zinc oxide (78) Perfumes and preservatives may be added Other types of eyeshadows are made in the form of sticks liquid suspensions and liquid dispersions Allergy when it occurs is usually due to the vehicle such as the ointment base or some of its special ingredients rather than the coloring agents used However instances of allergy have been reported in which the pigments used were thought to be responsible agents (79)

Eyebrow pencils Sticks pencils and crayons used for the eyes or brows consist mainly of paraffin to which pigments have been added The colors are similar to those of eyeshadows however they may be used in larger amounts Due to their simple composition allergy (fig 64) appears rela



Fig 64 Contact allergy to eyebrow pencil (courtesy of New York Skin & Cancer Unit)

tively rarely However Neuschuler (71) did report reactions in three cases from the use of colored eye crayons, but did not indicate their ingredients

Eye creams Eye tissue eyebrow and eyelash creams are basically similar in composition to other creams and may, on occasion, result in allergic reactions

Hair lacquers In an outbreak of dermatitis among users of hair lacquer pads the allergy was traced by Schwartz (80) to the synthetic resin used as a substitute for shellac More recently hair lacquers used as sprays have *become exceedingly popular Allergies from the polyvinylpyrrolidone* extender the shellac and the propellants may occur

perfumes used may cause reaction

As a result allergies to such products are not uncommon and especially involve the eyelids (figs 65 and 66)

Permanent wave preparations and hair straighteners Dermatitis



Fig 65 (*Left*) Contact allergy from hair dressing (brilliantine) (courtesy of Dr F S I) (*Right*) Contact allergy limited to eyelids from hair dressing (brilliantine) S I and M was Clin Opht 1952)



Fig 66 Contact allergy of eyelids from hair pomade (courtesy of Dr H L Thorpe)

from permanent waving may occur from the primary irritating effects of reducing agent formerly the sulfides now the thioglycolates used to often the hair or from allergy to gums and resins applied to hold the curl Hair straighteners formulated on a similar basis may be the cause of even more allergic reactions due to carelessness.

Cosmetic aids and implements Ocular allergy may occur not only from cosmetics themselves but from various aids and implements used

in their application Allergy to *powder puffs* especially those containing rubber has been observed Eyelash curlers have caused allergy due to their rubber content Medicated paper tissues such as those containing benzalkonium (Zephiran) have resulted in sensitivities Melamine resins in wet strength paper facial tissues napkins and towelling may cause contact allergy

Wearing Apparel

Since reactions to clothing normally are confined to the areas of the skin in direct contact with the offending material wearing apparel per se is of relatively little practical importance as a cause of ocular eczema Most such reactions are through finger contact However in women the putting on of a dress or slip has resulted in such sensitivity Allergy to *fabrics coming in direct contact with the face such as pillow cases occurs* more frequently

Fabrics Contact allergy to fabrics almost always is due to chemicals used in processing and finishing goods not the raw materials themselves Although unprocessed silk cotton and wool may play a role in atopic reactions such as atopic dermatitis and respiratory allergy they cause contact allergy only on the rarest occasions

As has been pointed out by Schwartz (16) allergic eczema to so called basic fabrics is often incorrectly diagnosed because of one of several errors *The first of these is that the sensitivity tests from which the diagnoses* are made are performed not with the actual raw materials but with gray goods already partially processed The second is the failure to differentiate between the physical irritation caused by woolly or rough fabrics and true allergy The same findings apply to synthetic fibers such as rayon (made from cellulose) nylon (made from synthetic resins) and glass fabrics as well as synthetic films and both natural and with rare exceptions synthetic rubber products The chemicals used in processing especially fabric finishes used for luster anti wrinkle and crease holding purposes and water proofing *all seem to be the agents responsible for* the allergy in most instances Similarly flame proofing moth proofing insecticides and antimildews are causes of allergic dermatitis Schwartz states that synthetic insecticides are usually primary irritants in strong concentration while natural insecticides are potent sensitizers

When dyes cause dermatitis Schwartz has found that it is usually due to a faulty process of dyeing whereby a chemical or a dye intermediate which should not be present remains in the fabric An idiosyncrasy to the dye itself is less common but is apt to occur if one of the known sensitizing dyes is used This is especially *likely to happen if the dyes* tend to bleed or come out of the fabric easily a situation influenced by

the pH of perspiration and the fat content of the skin Waldbott (18) states that the recent popularity of loud sport shirts for men has resulted in more contact dermatitis Wherever preliminary washing of new garments is possible, as for example with socks stockings and shirts allergy may be avoided

Laundering and dry cleaning materials All substances used for laundering such as soaps starches bleaches and laundry marks may cause allergies Dhobie mark dermatitis (81) occurred in the U S Army in India during World War II as a result of using the fluid from the nut of the ral or bella gutta tree for marking clothes Thus the entity known as dhobie itch might well be an allergic reaction rather than a fungal infection as generally believed

Similarly chemicals used in dry cleaning may cause allergic reactions

Leather goods Contact allergy to leather (artificial and genuine) likewise is due to the manufacturing process Concerning shoes while many chemicals involved in their manufacture might be implicated in dermatitis of the feet as regards the eyelids only shoe polishes dyes and tanning and preserving agents are likely to be responsible In Shaw s (82) series of seven cases of dermatitis due to shoes brown polish appeared to cause the reactions in three cases One patient developed eczema involving the face as a result of shining his shoes with such polish Patch tests were positive Peterkin s (83) case is even more interesting His patient noted swelling of the eyelids every Sunday it vanished in two to three days He himself finally realized that his only regular habit on Saturday night was to polish the brown shoes he wore only on Sundays Patch tests to brown shoe polish were strongly positive Upon stopping the practice the condition ceased to recur

Furs Furs are more apt to cause allergic dermatitis of the eyelids than other articles of apparel because of both the locations where they are worn and the dyeing and tanning agents used in manufacture Until recently poor dyeing permitting the leaching by perspiration and moisture was the basis for most sensitivities Greater care is now exercised in this regard such as insuring that careful and complete oxidation of the dye generally used (paraphenylenediamine) with thorough removal of any excess remaining is performed As noted previously paraphenylenediamine in itself is considered comparatively non sensitizing its first oxidation product quinone diimine is the actual sensitizer Other oxidizing dyes such as aniline black and orthoaminophenol may also cause dermatitis as do chrome mordants

Jewelry Allergy of the skin of the eyelids from jewelry may occur as the result of direct contact such as the continual rubbing of a finger ring against the lid through habit Bracelets lockets wrist watches and their



Fig 67 Contact allergy to nickel probably jewelry (courtesy of New York Skin & Cancer Unit)

straps are all much less likely to come into direct contact with the eyelids Allergy, however, may occur indirectly through fingering the responsible object and then rubbing the eyelids Eyelid contact allergy from the handling of metallic objects is well known Such an occurrence in a woman who handled many pennies and nickels and developed allergy to nickel has been mentioned previously It should be remembered that most jewelry and metallic ornaments are alloys Thus the allergy may be due to only one of the metals used Nickel (fig 67), cobalt, platinum chromium, aluminum, and gold have all been reported as causing allergic dermatitis A gold ball implant following enucleation has been reported to cause allergy, as may plastic prostheses Allergy from both gold-filled and plastic spectacles is discussed immediately below

Spectacle frames. Ocular eczema due to the use of spectacles is naturally of considerable interest to ophthalmologists Although a number of reports are available, such contact eczema appears relatively rare and even less commonly reported at the present time than a decade ago Whether this is merely fortuitous or due to improvements in methods of manufacture is a matter of conjecture Two types of eyeglass frames are known to cause contact allergy 1) metallic especially white gold, due to the nickel content, and 2) plastic (horn rimmed), probably due to various chemicals used in the manufacturing process

The distinguishing feature of the eruption is its distribution in general the major points of contact of the eyeglass frames with the skin are outlined Thus, the dermatitis first becomes apparent about the bridge of the nose, the temples and behind the ears (fig 68), later the eyelids proper,



Fig. 68. Contact allergy to plastic eyeglass frame (courtesy of New York Skin & Cancer Unit)



Fig. 69. Contact allergy of eyelids from nickel alloy in gold-filled eyeglasses (courtesy of Dr. H. F. Thorpe)



Fig 70 (*Top*) Contact allergy to plastic portion of eyeglasses (S h & M[illegible] Clin Ophth 1953) (*Bottom*) Same patient without glasses (courtesy of Dr J S h & Dr E Mawas)

especially the lower lids become diffusely inflamed and may be markedly swollen (fig 69 and 70) Even the conjunctiva may become involved presenting the typical picture of allergic dermatoconjunctivitis The eczematous reaction may be very acute of the weeping variety, often however it is drier and more lichenified The importance of perspiration as



Fig. 71. Positive contact patch test to offending eyeglasses (Different patient) (courtesy of Dr F Mawas)

a factor in the causation of the allergy is well recognized and fits in with our experiences in other types of contact allergy. While patch tests on other parts of the skin are usually positive (fig 71) on occasion only the involved facial areas may give such positive reactions. Observers therefore should not be misled by negative skin tests but be guided by clinical findings. Sometimes undiagnosed instances of eyelid eczema clear dramatically when chance loss of the offending eyeglasses results in the substitution of another type of frame which is nonallergic.

Metallic frames. Allergy to both platinum and solid gold frames does occur but is most uncommon. Nickel is the major sensitizer. Ocular eczema due to the nickel in white gold spectacle frames was reported by Lain (84) in 1931. In two of his three cases only the temples and ears were involved because the spectacle bridge was of different metal and the nose therefore did not react. Lain concluded that perspiration acted electrolytically on the nickel in the frame forming allergenic nickel salts. Substitution of solid gold instead of gold filled frames relieved the eczema. McAlester and McAlester (85) reported three additional cases of allergy to white gold frames somewhat later in the same year. They used a nickel coin successfully for patch testing—not exactly the best method since other metals are present in such coins but an easy and certainly suggestive one. Dermatoconjunctivitis as severe as that due to atropine was encountered in one of their cases. Erythematous lesions of the alae of the

nose and the ears due to the eyeglasses recurred when the patient rubbed a white gold watch and then pulled on his nose. Other interesting reports have been published by Fox (86) and Cornish and Stewart (87). The latter authors observed five instances of spectacle frame dermatitis in a study of eleven cases of nickel dermatitis. In three of the eleven cases patch tests were negative when done elsewhere on the skin, but were positive at the original site of the eruption. They too emphasized the importance of perspiration. Six additional cases of nickel dermatitis due to the wearing of British Army spectacles were reported by Taylor and Fergusson (88) in 1945. Their studies brought out the fact that the bridges and end pieces of such frames contain twice as much nickel as other portions (that is twenty-five per cent), explaining the location of most eruptions. When the frames were placed in water, the solutions, tested chemically, revealed no nickel; in one per cent sodium chloride solution traces of nickel were found. This indicated that the allergic reaction needed the intermediary of sweat for its occurrence.

Plastic frames. The problem of contact allergy to plastic spectacles is much more complicated. Whereas with white gold glasses all the evidence points to one entity (nickel allergy), with synthetic frames on the other hand so many factors appear to enter into the picture that the allergy may be due to many different causes. Commonly used ophthalmic plastics include cellulose nitrate ("zylonite"), cellulose acetate, cellulose acetate butyrate and methyl methacrylate (lucite or plexiglas). Different processes are used for the production of each of these types. The exact details of their manufacture are not readily obtainable, but it is clear that the many chemicals employed in the making, processing and dyeing of the plastics, as well as chance impurities or defects in manufacture that occur at times and the plastics themselves, all may provoke allergies. Apparently the plasticizers used are the major offenders, the actual plastics are said to be relatively harmless. Thus methyl methacrylate monomer is known to be a skin sensitizer, but in the finished eyeglass frames there should be insufficient monomeric methyl methacrylate left to cause allergy. The incidence of allergy to plastic frames would appear to be decreasing, probably due to improvements in the manufacturing process.

Sutton's case (89) of allergy to plastic frames occurred in a patient who had worn new frames for only one half hour; a twenty minute contact of the frames with the forearm was strongly positive within a few hours. The reaction occurred only with the front portion of the spectacles. The bows or temples caused no reaction and the patient was not sensitive to another

(90) concluded that either artificial resins or aniline dyes ...

lergy in his three cases Berkoff's (91) careful investigation of the cause in his case indicated that plasticizers used to soften the product were the responsible allergens not the dyes or the basic cellulose acetate itself At the time of his report (1938), twenty four plasticizers were in general use for this purpose of the four he could obtain for testing in his patient, two (tricresyl and triphenyl phosphate) were strongly positive At the present time more ingredients especially plasticizers are utilized However Swinney (30) mentions two instances of allergy to red plastic frames not to plastic frames of other colors Home (do it yourself) tinting of old plastic frames as for example with fingernail polish is of course another cause of contact allergy due to eyeglass frames

Miscellaneous Causes

Rubber Allergies from natural rubber are usually not due to the rubber itself but to compounds such as accelerators and antioxidants placed in the rubber and to impurities in manufacture However synthetic rubber does contain sensitizers not found in natural rubber

Plants Reference has been made already to the importance of plants as a cause of allergic dermatitis of the eyelid Although the reaction generally occurs through direct contact it may occur indirectly as a result of handling exposed clothing or stroking the hair of an animal who has been in the open Cooke (92) reports air borne contact from standing in the smoke of burning brush as the allergen adheres to the carbon particles in a highly active state Although dermatitis has been reported from hundreds of plants wood flowers fruits and bulbs most cases are the result of poison ivy (fig 72) poison oak poison sumac Japanese lacquer made from similar plants liquid from cashew nuts and others of the family Anacardiacea according to Schwartz In addition primula geranium



Fig 72 Contact allergy to poison ivy (courtesy of New York Skin & Cancer Unit)



Fig 73 (Top) Seasonal dermatitis contact allergy to ragweed pollen Dermatitis occurred only during the hay fever season period of pollination The hay fever present in this patient was only coincidental (courtesy of Dr H E Thorpe) (Bot

chrysanthemum tulip and gladiolus are important allergens The active ingredients of most of these plants are polyhydric phenols of essentially similar chemical structure They are basically primary irritants in strong concentration They are found in the root stem leaf flower or pollen Certain plants such as bergamot buckwheat and some grasses are photosensitizers

Contact dermatitis to ragweed—pollen (fig 73 (Top)) or to the plant itself (fig 73 (Bottom))—appears entirely unrelated to ragweed hay fever In fact when the two occur together it is purely coincidental In



Fig 71 Contact allergy to household detergent

ragweed dermatitis the allergic reaction is due to the lipoid fraction in hay fever it is due to the protein fraction The dermatitis is a typical delayed allergic contact reaction with none of the atopic characteristics of hay fever

Household products. Eczema of the eyelids due to household products includes reactions to varnishes shellacs cleaning solutions and other similar substances New furniture new upholstery or new paint should be suspect in difficult cases The popularity of soapless detergents has resulted in many contact allergies (fig 74) especially of the hands (detergent hands) It should be remembered that the numerous silicone compounds used as hand lotions in the treatment of detergent hands may in themselves result in eye allergies

Occupational dermatoses of the eyelids While most occupational dermatoses are due to primary irritation (fig 75) rather than allergy occupational contact allergy causes from five to ten per cent of all instances of ocular eczema This occurs not only because the eyelids are directly exposed but because finger to eyelid skin contact is so very common The legal compensability of such contact reactions is now widely accepted in most countries In fact while certain types of workers such as those in the fur industry have long been known to develop allergies it is now clear that the list of industrial allergens is almost limitless These are mostly chemicals of which the entire gamut inorganic as well as organic natural and synthetic used in industry especially dyes metals such as nickel



FIG 75 Depigmentation from rubber goggles This was due to the irritant not allergic effect of monobenzyl ether of hydroquinone (courtesy of Dr I I Lubowe)

lead mercury beryllium and selenium lacquers varnishes dusts sprays inks woods drugs glues disinfectants explosives and many others can cause allergies

Certain types of workers are especially susceptible to contact dermatitis According to Schwartz (16) these include chemists photographers agricultural and other workers in contact with plants florists fruit and vegetable handlers cannery workers exterminators operators on fabrics treated with irritant chemicals rubber compounders munition workers dye manufacturers and those in contact with dye intermediates

LEGAL ASPECTS

A manufacturer is generally not held liable for an allergic reaction occurring from the use of his product However if it can be shown that the allergy is the result of a fault in manufacture or of impurities introduced thereby then such liability might be established Before new cosmetics are introduced standard testing and trials are performed

Similarly a physician is not liable under ordinary circumstances for contact allergies occurring in his patients It is assumed of course that he uses reasonable care and judgment in the prescribing of such medicaments

TREATMENT

Elimination of the cause The basic principle in the treatment of contact eczema of the eyelids is the elimination of the offending substance

if it has been identified, or of all possible offenders if no definite cause has been established. Largely with the help of a careful history-taking a fairly shrewd guess may usually be made as to the underlying cause. Even if patch tests are negative, it is often wise to stop the use of all suspected agents, indeed all likely sensitizers, for the time being. Despite the fact that the sensitizing substance has been discovered and apparently completely eliminated, at times a patient may unwittingly continue to be exposed through indirect contact. This is especially so in regard to allergies due to plants, chemicals and metals.

Management of cosmetic allergy. When it appears that the allergy is due to a cosmetic, unless the evidence points strongly to a particular one it is best for the patient not to use any at all until the eczema disappears. Since this is easier said than achieved, the physician must often settle for a second best objective. He may allow the patient to use hypoallergenic powder and lipstick, but no fingernail polish, no cosmetic used about the eyes nor any hair shampoo. When the dermatitis has cleared, then desired cosmetics may be resumed, preferably one at a time, until the guilty one has been established. Often, since hypoallergenic products prove satisfactory and are utilized thereafter, the specific allergen is never demonstrated. The rare patient who cannot tolerate those hypoallergenic preparations commercially available need not be condemned to a bleak and pale existence; the manufacturers are ready and willing to make special products for such an unhappy individual.

Hypoallergenic cosmetics. The introduction of hypoallergenic cosmetics has been of great help in the management of allergies to cosmetics. Previously the patient had no recourse except to try one brand after another in the hope of finding a harmless product, or else not use that form of cosmetic at all. Hypoallergenic preparations utilize especially refined ingredients for the purpose of eliminating those impurities that may cause reactions in rare individuals. Another basic aim in their composition is simplification, where one substance will serve the purpose of two similar ones; the chances of allergy are lessened. Moreover, if it should occur, the harmful component is more readily recognized. Thus hypoallergenic cosmetics may contain only half the ingredients of the usual products, eliminating any of the more likely sensitizers such as lanolin, cocoa butter, preservatives, organic dyes and perfumes (45). Furthermore, on the basis of immunochemical studies discussed earlier in this chapter, preference where possible is given to the use of saturated vegetable oils rather then unsaturated compounds, to the esters of phenols and to the avoidance of para linkages. An important by-product of this systematized search for safer cosmetics for special individuals is that all cosmetics available, not necessarily only hypoallergenic ones, are improved so that they become less likely to cause allergies.

Drug therapy Rather than aggravate an already hyperergic skin which now may react allergically to medicaments it can tolerate at other times it is generally best to use little or no local therapy In the past many mild cases of allergic dermatitis were made severe ones by the injudicious use of ointments or other products containing sensitizing substances such as tar and related chemicals phenol products anesthetics and antiseptics containing mercury Nowadays antibiotic, sulfonamide and antihistaminic ointments have been found to be the major causes of secondary allergies in such cases Soap and water should be avoided, gentle sponging with olive oil may be allowed

Steroids The systemic use of corticotropin (ACTH), and the corticosteroids is generally not necessary but such therapy is valuable in severe reactions Since the allergy soon subsides the hormones need be given for only a few days and thus are rarely contraindicated Local therapy is best limited to hydrocortisone in the ointment form (one to two and five tenths per cent) which is usually very effective It should be remembered however that even cortisone hydrocortisone and other steroids may cause allergy and that some persons are allergic to ingredients of ointment bases especially lanolin If a secondary infection is suspected systemic antibacterial therapy with tetracycline derivatives or sulfonamides appears preferable to their local use even in the numerous combinations with steroids now available

Antihistaminics As mentioned previously not only are antihistaminics ineffectual in contact allergy but they may result in secondary allergies when used as ointments Because of this such ointments are no longer approved Only where a proved allergy of the immediate variety such as ragweed hay fever is present and may play a role in the perpetuation of the contact allergy (a rare happening) are antihistaminics indicated and then only orally

Sedatives It is important to procure for the patient adequate rest at night during the acute phase of the contact dermatitis It is necessary to use sedatives during the working hours only in the unusually disturbed and nervous patient Tranquilizers are useful In any event the course of the dermatitis is short enough nowadays not to require the prolonged use of sedatives and hypnotics such as are advocated by many for atopic dermatitis

Desensitization Few contact agents lend themselves to desensitization procedures It is claimed that the only ones that do are fatty substances Most desensitization for contact allergy is done against plant oils such as poison ivy ragweed timothy and tree oil extract This procedure generally lies in the province of the allergist

X ray The use of radiotherapy is becoming much less frequent for con

tact allergy of the eyelids because of the great value of the steroids In those cases where an allergy is superimposed on a dermatosis such as atopic and seborrheic dermatitis for which x ray is a valuable form of treatment or when a chronic lichenified lesion has developed roentgen therapy still has a place

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13

ECZEMA OF THE EYELIDS DUE TO OTHER CAUSES

As noted in the introduction of the previous chapter, the emphasis that has been placed on contact allergy as the cause of eczema of the eyelids has tended to make physicians less alert to the fact that other types of eczematoid dermatitis, often very similar in appearance, do occur and must be differentiated if therapy is to succeed. In fact, while acute eczema of the eyelids is almost always the result of allergic contact reactions, the much more troublesome chronic forms of eczema appear more often than not to be due to causes other than contact allergy.

The major types of eyelid eczema encountered may be classified as follows: 1) allergic eczematous dermatitis secondary to contact allergy; 2) infectious eczematoid dermatitis, of which staphylococcal eczema secondary to infection of the eyelid margins with pathogenic staphylococci is by far the most common variety; and 3) certain generalized dermatoses such as atopic dermatitis, neurodermatitis, seborrheic dermatitis and psoriasis, in which eczematized lesions occur primarily on the eyelids but where careful search will reveal diagnostic lesions elsewhere (1, 2). In each instance the treatment is entirely different; incorrect therapy based on the wrong diagnosis not only will yield no benefit but may at times result in serious aggravation of the original dermatitis.

INFECTIOUS ECZEMATOID DERMATITIS

Eczematoid dermatitis of the eyelids may arise on an allergic basis as a complication of bacterial, fungal or other microorganismal infection present elsewhere. The eyelid skin itself is not directly invaded by organisms. This basically allergic response to infectants must not be confused with the numerous types of dermatitis resulting from direct invasion of the skin of

the eyelids by many bacteria viruses and fungi The latter are entirely distinct and not germane to the subject Allergic reactions of the eyelids due to bacteria generally are the result of neighboring infection of the adnexae although rare syphilids and tuberculids need not follow this pattern In fungal infections however the original focus may be far from the eye and entirely unrelated to it In either event the eczema appears to be in a large measure a manifestation of microbial allergy While microbial dermatitis elsewhere on the body may result from a variety of infectants including Staphylococcus Streptococcus and *F coli* (3) as far as the eye lids are concerned the important bacterium involved is the Staphylococcus On rare occasions streptococci are responsible Eyelid eczemas due to fungus sensitivity an unusual occurrence to begin with appear mainly as *trichophytids or monilids All types of infectious eczematoid* reactions appear prone to secondary contact type allergies especially from medicaments Since the reverse also happens—that is the secondary infection of primarily allergic dermatitis—diagnostic problems may arise About the eyelids however fewer such differential difficulties should occur because the only type of infectious eczematoid reaction of practical importance encountered—staphylococcal eczema—generally is associated with other ocular findings that afford valuable diagnostic clues

STAPHYLOCOCCAL ECZEMA

The importance of staphylococcal infections of the eyelid margin and conjunctiva as a major cause of eczema of the eyelids has not received the emphasis it deserves While dermatitis actually is a relatively infre*quent complication of* such common infections recent experience indicates that the condition is the most frequent cause of chronic eyelid eczema encountered yet because its importance is not generally appreciated it is often overlooked

The simpler term staphylococcal eczema (4) is preferable to the rather redundant and awkward infectious eczematoid staphylococcal dermatitis which has been used hitherto to describe dermatitis occurring from superficial staphylococcal infection Whether the *infection is secondary* to skin pathology as may occur in the hand (5) or is primary as generally seems to be the case around the eyes is relatively unimportant from the therapeutic viewpoint in either event specific antibacterial treatment in *all its forms is indicated in contrast to the nonspecific symptomatic ther*apy used for other types of eczema Proper diagnosis is therefore of the utmost importance as such aggressive treatment wrongly applied to the hypersensitive skin of contact allergy or to the acute manifestations of other dermatoses would aggravate them immeasurably The bland regime indicated in nonbacterial eczemas on the other hand if wrongly used in

the infectious cases merely serves to provide a better climate for the bacterial process

Diagnosis

Many unrecognized recurrent cases of staphylococcal eczema (Plate II, fig 6) of the eyelids are treated unsuccessfully for years as instances of contact allergy One cannot distinguish between the two conditions on the basis of the character of the dermatitis as they look very much alike (figs 76 and 77) What is required for the diagnosis and successful treatment of staphylococcal eczema is the demonstration that the focal point of the process is not the skin but instead is the eye and its adnexae When this is demonstrated and proper treatment instituted the eczema which is a secondary complication gradually disappears The key to the diagnosis is routine detailed ophthalmologic examination both clinical and bacterial This almost always will reveal the basis for the dermatitis even if the primary focus is obscure such as a minute abscess of a meibomian gland The following findings differentiate staphylococcal eczema of the eyelids from the allergic variety (a) blepharitis with scaling and often ulcers of the eyelid margin (b) meibomitis either diffuse or focal (c) superficial epithelial keratitis involving the inferior half of the cornea readily seen on slit lamp examination after staining with fluorescein considered as pathognomonic of staphylococcal conjunctivitis (d) strongly positive conjunctival and lid margin cultures showing many toxin producing staph



Fig 76 Staphylococcal eczema of the eyelids (Theodore (1))



Fig 77 Allergy to bacitracin (note superficial resemblance to fig 76) (Theodore (1))

ylococci, often entirely out of proportion, numerically, to the objective clinical findings, and (e) absence of eosinophiles in epithelial scrapings—which instead, usually reveal neutrophiles and *staphylococci* especially on the lid margins

It should be emphasized that cultures of the lid margin and conjunctiva which are positive for pathogens (fig 78) are not a normal occurrence, they serve to confirm the clinical findings in patients suffering from staphylococcal dermatitis, that the primary trouble is ocular, not dermatologic

involved ec

n are found

In view of the frequency of *staphylococcal infections of the outer eye* as against the relatively rare occurrence of staphylococcal eczema it would *seem that a special basic diathesis or set of circumstances is necessary for* the condition to develop The dermatitis is found predominantly in middle-

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lacrimation

or even frank keratoconjunctivitis sicca may be present The occurrence of mild hypothyroidism and especially a seborrheic diathesis both with dry skins appears to be more than coincidental An interesting phenomenon is the presence of verrucous lesions which become prominent in these



Fig 78 Cultures of conjunctiva and eyelids (patient in fig 76) revealing numerous colonies of pathogenic *Staphylococcus aureus* growth in form of M (top left quadrant) was obtained from expressed meibomian secretion (Theodore (1))



Fig 79 (Same patient as in fig 76) Complete cure of staphylococcal eczema At this time bacterial cultures and skin tests were negative

patients It would appear that these factors in addition to irritation from cosmetics may predispose such patients in the absence of atopy to hyper sensitivity or heightened susceptibility to bacterial products

Mechanism

The concept that local infections by bacteria could cause eczema is not new yet it gained little general acceptance until recently Even before the apt if unwieldy term infectious eczematoid dermatitis had been given to the entity by Engman in 1902 (6) other investigators had stressed the role of bacterial infection in its causation *Within the last twenty years* however more and more dermatologists have come to appreciate the im portance of either primary or secondary bacterial infection especially staphylococcal in the production and perpetuation of eczema In a previous chapter the general tendency to underrate the Staphylococcus was men tioned *The important role that this organism plays in the pathogenesis* of many common external diseases was overlooked primarily because in vestigators did not differentiate pathogenic toxin producing strains from the ubiquitous nonpathogenic varieties to be found on cultures of the con junctiva and other mucous membranes the eyelids and the skin The fact *that the Staphylococcus produced exotoxins had been demonstrated over* fifty years ago however these toxins received surprisingly little attention (except from the French) until twenty five years ago Burnet s funda mental work in 1929 is the basis of modern concepts concerning these toxins as well as for the therapeutic use of staphylococcal toxoid and antitoxin Thygeson *(8–10) was the first in the field of ophthalmology to stress the* etiologic importance of such toxigenic staphylococci in blepharitis mei bomitis conjunctivitis especially the chronic variety and keratitis re vitalizing our concepts and treatment of these long neglected conditions He has pointed out the significance of such staphylococcal infections in *the causation of eczematoid dermatitis of the eyelids*

Of the many toxic products elaborated by the Staphylococcus the ther molabile and filterable exotoxin which contains a dermonecrotizing factor is the most important A safe yet antigenic toxoid is made by treating exotoxin with formalin or other products However other exotoxins as well as endotoxins and *other bacterial products such as bacterial protein* likewise are antigenic and seem to play a role in staphylococcal allergy

Pathologic processes due to Staphylococcus toxin may arise in the eye through either of two mechanisms 1) direct toxic action or 2) allergy to the toxin Certain studies support the first concept Allen (11 12) has produced conjunctivitis and *the superficial keratitis characteristic of staph* ylococcal conjunctivitis by instillation of staphylococcal toxin His ex perience (13) with the beneficial effects of antitoxin in corneal infection

due to Staphylococcus is additional evidence for direct toxic action. On the other hand, the work of Woods (14, 15) and Burky (16) and our own observations indicate that hypersensitivity to Staphylococcus toxin results in chronic conjunctivitis. Moreover, others like Braley (17), have felt that allergy to the toxin is a major factor in a number of ocular inflammations, such as marginal infiltrates of the cornea.

There is no question that allergy to other products of the Staphylococcus occurs as well. Skin reactions to staphylococcal filtrates are elicited in about sixty-five per cent of normal individuals and in nearly all persons with staphylococcal infections. However, no reactions are obtained in newborn infants. Since the reaction appears to develop without relation to the amount of antitoxin in the blood, it would seem to indicate an allergic state. Furthermore, type A (pathogenic) polysaccharide produced by staphylococci causes an immediate wheal and erythema upon intradermal injection in patients with staphylococcal infection. A delayed type of response occurs upon injection of the protein common to both type A and type B staphylococci (18).

The significance of positive reactions to intradermal products has been discussed in chapter 4. For the sake of continuity some important points are repeated here. Our clinical observations support the experimental work of Gernez and Pannequin (19), who feel that intradermal injection of toxin causes two phenomena—one toxic, the other allergic. The toxic reaction, being reciprocally dependent on the blood antitoxin titer, provides an index of immunity to Staphylococcus infection; the allergic reaction, of shorter duration, is uninfluenced by antitoxin and may be elicited by dilute toxin, heated toxin, or toxoid. The intradermal reaction to dilute toxoid offers, within limits, an index of allergy to Staphylococcus proteins and to other staphylococcic products. Marked reactions to dilute toxoid or vaccine appear diagnostically significant of allergy. These reactions may be of both the immediate and the delayed types, and on rare occasions are especially marked with autogenous vaccines as compared to toxoid. An allergic correlation of positive toxoid reactions with past or present staphylococcal infection has been found by Wagner and Maly (20).

A dual mechanism may be postulated for the production of staphylococcal eczema. The first mechanism appears to be the direct toxic action of the dermonecrotizing exotoxin of the Staphylococcus. The second mechanism, allergy to various staphylococcal products, including exotoxins, endotoxins and staphylococcal proteins, seems, however, to be the more important one on the basis of both experimental and clinical observations. Repeated injections of toxin induce an allergic response in rabbits. The work of Hopkins and Burky (21) suggests that a more complex type of bacterial allergy may be responsible for the production of the eczematoid

dermatitis All were sensitive on skin test to Staphylococcus toxin and on culture most lesions revealed pathogenic staphylococci They used staphylococcal toxin injections with good results and concluded that the dermatitis was due to local hypersensitivity to the patient s own skin keratin brought about by the liberation of Staphylococcus toxin plus trauma at the site of the lesions Some confirmation of this theory is afforded by the work of Hecht Sulzberger and Weil (22) who showed in 1943 that Staphylococcus toxin exerted a synergistic action when injected coincidentally with rabbit skin antigen in producing antibodies (precipitins) to homologous skin in rabbits *Ulbricht (23)* working with toxins obtained from bacteria cultures from eczematous lesions concluded that nummular foci of eczema appear as an expression of sensitivity (allergy) to toxin obtained from the primary focus *He noted further that the eczematogenous* manifestations were particularly apparent with staphylococci and that the toxin not the presence of living bacteria caused the reaction The acid *mantle of the skin was not protective in this regard He called attention* to the existence of special dermatropic strains of staphylococci

Storck (24) in his studies on bacteria in eczema concluded that autosensitization to bacterial products played an *important part in its production* Although he found that the Staphylococcus was the major cause he thought that the Streptococcus and the *E coli* were likewise important This was not a study of eyelid eczema per se He cultured *Staphylococcus aureus* in ninety two per cent of patients and elicited positive patch tests in sixty eight per cent The specificity of the individual reaction to autogenous filtrates indicated an allergic mechanism Eczema could be reawakened by bacterial patching The good results obtained by specific vaccine therapy with no correlation with the bactericidal titer of the serum and whole blood also pointed to the allergic basis for the eczema

One may assume therefore that eczema occurs in staphylococcal infections as the result of a combination of two mechanisms 1) the direct action of dermonecrotizing toxin, and 2) allergy to all types of staphylococcal products or to a Staphylococcus toxin skin *protein complex* Vidal and Weil (25) feel that faulty lipid metabolism plays an important role in such allergic reactions

Treatment

While the immediate objective of treatment as far as the patient is concerned is to cure the eczema the physician s goal should include the elimination of the underlying infection This may prove very difficult If it is not accomplished however recurrences of the dermatitis are not infrequent Therapy is based primarily on two methods 1) the use of antibacterial agents and 2) injections of toxoid and vaccine when *in*

dicated The patient however, may be conditioned by an unusually sensitive skin so that allergies to antibiotics sulfonamides antiseptics and ointment bases are particularly common Furthermore bacterial resistance to antibiotics is often encountered The systemic use of antibiotics or sulfonamides if tolerated is advised however it is not in our experience especially effective—although dermatologists have found these medicaments most efficacious in infectious eczematoid staphylococcal dermatitis occurring elsewhere in the skin probably because the infection is not as deepseated Their local use seems to give better results Ten per cent sodium propionate (pH 6.0) is safe and often valuable Where meibomitis is present expression of the lid glands is useful The value of topical applications of two per cent silver nitrate over the lid margins the entire involved skin of the eyelids and especially any fissures that may be present should be stressed Sometimes dramatic improvement follows such treatment yet care must be taken against too generous or too frequent use as direct primary irritation of the already inflamed skin sometimes does occur

Hydrocortisone appears to be the most effective of the corticosteroids Its local use often results in rapid improvement in the dermatitis after the underlying bacterial process is controlled but not necessarily eliminated Newer products such as prednisone and prednisolone are also useful

Toxoids and vaccines are reserved for the most resistant cases and for those patients in whom bacterial allergy or an allergic complex appears operative as manifested by intradermal reactions to dilute toxoid It is now generally accepted that for the production of Staphylococcus antitoxin the antigenic properties of toxoid are vastly superior to those of vaccines and that toxoid is usually far more successful in the treatment of most subacute or chronic cutaneous staphylococcal infections (26) Clinical improvement is accompanied by an increased titer of circulating antitoxin—which however varies with different individuals The immunity derived is antitoxic no antibacterial effects are obtained Vaccines on the other hand stimulate the formation of other types of antibodies such as agglutinins but little or no antitoxin is formed. Yet on occasion they appear clinically more effective than toxoid Therefore while the use of Staphylococcus toxoid is always indicated in resistant staphylococcal infections it would appear desirable to employ vaccine as well (27) Stock vaccine toxoid combinations are commercially available However on the theory that bacterial allergy is present it is felt that in long standing instances of infectious eczematoid staphylococcal dermatitis autogenous vaccine is preferable as all the autogenous bacterial proteins polysaccharides and other products are thus utilized for desensitization By such combined use of toxoid and autogenous vaccine

better results are apt to be obtained The best therapeutic results of vaccination often occur in individuals with the most marked initial reactions as noted by Thygeson (28) If clinical improvement is paralleled by negative conjunctival and lid margin cultures and reduced intradermal reactions recurrences are unlikely In a patient who could not tolerate any form of biologic therapy because even minute doses of autogenous vaccine caused arthritis with swelling of the fingers the eczema cleared mainly due to the use of silver nitrate Cultures and skin reactions remained positive and the eczema recurred in mild form wherever local therapy was discontinued Although the antitoxin titer is usually elevated after vaccination this is not always so instances have been reported in which minimal intradermal reactions to toxoid are present in previously positive individuals despite a very low antitoxin titer, indicating that *allergic desensitization to toxoid or toxin plays an important role*

Sulzberger (29) has made some interesting observations concerning the general diagnostic and therapeutic value of Staphylococcus toxoid He found that immediate wheal and flare reactions occurred in practically

rived from the Staphylococcus it was in all probability caused by an allergic skin sensitivity to products of the Staphylococcus Repeated injections of toxoid increased the resistance of the skin to toxoid and hyposensitized the skin to toxoid Toxoid injections did not uniformly increase the antihemolysin titer of the blood serum, nor did the lessened skin reactions run absolutely parallel to the increased blood titer Subcutaneous injections seemed to give better results both therapeutically and serologically than did intracutaneous injections These observations would tend in general to support our own ideas on this subject

It seems advisable *to base initial dosages on the reaction to small intra*
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generally appear preferable Experiences with a new purified and adsorbed toxoid by Tasman and coworkers (30) indicate that maximal antitoxin titers are attained with it after only a few injections regardless of intervals between injections with no undesirable side reaction

ECZEMATOID DERMATITIS DUE TO FUNGAL ALLERGY

Eczematoid dermatitis may appear at local sites as id manifestations secondary to bacterial or fungus infections elsewhere in the body As defined by Sulzberger (31) such an id reaction is a secondary manifestation appearing in a specifically altered (allergic) tissue produced by microorganisms emanating from a distant focus and/or the allergenic products of such organisms These microorganisms need not be demonstrable in the id lesions and in fact only rarely are

While such allergic reactions due to fungi and their products are not uncommon in other parts of the skin according to our own studies and those of Thygeson (32) they appear to involve the eyelids only rarely They are encountered mainly as dermatophytids such as allergies to trichophyton epidermophyton and micro poron and as moniliids or sensitivities to Monilia (Candida) Despite the frequency of dermatophytosis of the feet and the not uncommon occurrence of dermatophytids of the hands in the United States as well as of moniliasis ocular id reactions (fig 80) are uncommon However Hanabusa (33) in Japan has stressed the importance of fungus allergy and Fazakas (34) in Central Europe the importance of fungus infection as causes of ocular eczemas If we may be guided by our own experiences in the New York area ringworm and monilial infections of the eyelids and conjunctiva are very rare indeed

The allergy is generally of the delayed type although immediate reactions occur The value of positive skin reactions is limited to some



Fig 80 Trichophytids of face and eyelids (courtesy of New York Skin & Cancer Unit)

TABLE 8

Differential diagnosis of common causes of ocular eczema

	Contact Allergy	Staphylococcal Eczema	Atopic Dermatitis	Seborrheic Dermatitis
Personal and familial history of allergy	Not essential	Not essential	Usually positive for hay fever, asthma, urticaria and other atopies	None
Other pertinent history	Recent exposure to allergenic substances	Previous staphylococcal infections	Previous infantile dermatitis, recurrences	Previous seborrhea
Bilaterality	Often unilateral	Often unilateral	Always bilateral	Almost always bilateral
Character of dermatitis	Moist, acute or subacute, with varying degrees of erythema, edema and vesiculation	Moist, acute or subacute, with varying degrees of erythema edema and vesiculation	Dry, papular and lichenified	Dry, erythematous, non vesicular, greasy scales
Associated dermatitis elsewhere on body	None	None	Antecubital, popliteal sides and back of neck, and mouth	Scalp, forehead, eye brows, nasolabial folds, retroauricular, presternal
Lid margins	Involved as part of process, not, in itself, distinctive	Ulcerative blepharitis and meibomitis present	Involved as part of the process, not in itself distinctive	Seborrheic squamous blepharitis
Conjunctiva	Usually not involved unless conjunctival contact occurred (allergic dermatoconjunctivitis due to medicaments)	Definite, severe papillary conjunctivitis	Usually not involved	Usually not involved
Cornea	Rarely involved	Frequent involvement by superficial punctate keratitis of lower half of cornea (seen by slit lamp)	Rarely involved	No definite involvement

Cultures	Usually no significant growth	Toxigenic Staphylococcus grown from conjunctiva, lid margins and meibomian secretion	No significant growth	No significant growth
Epithelial scrapings	Conjunctival eosinophilia if allergic dermatoconjunctivitis present	Cocci and neutrophiles on lid margins	Rarely conjunctival eosinophilia	Budding yeast (*Pityrosporum ovale*) on lid margins
Intradermal and scratch tests	Negative	Usually negative except for marked reaction to Staphylococcus toxoid	Few to many positives	Usually negative
Patch tests	Often positive	Negative	Negative	Negative
Treatment	Removal of cause steroid blocking agents	Antibacterial agents toxoid and vaccine injections, steroids helpful as adjuvants only	Steroids other nonspecific treatment desensitization not especially helpful	Sulfur mercury other nonspecific agents

extent by the fact that they are observed so frequently in the United States probably because of the widespread prevalence of fungus skin infections A negative reaction however is diagnostically significant No evidence of mycotic infection is found in the eczematized eyelid skin but is usually demonstrable at the primary site of infection When the original focus is successfully eliminated the eyelid eczema disappears, although cutaneous sensitivity to the specific fungal product remains It would seem that local steroid therapy should be effectual in these essentially allergic reactions

An interesting study of eczematoid monilid (candidid) of the eyelids was published by Ruiz Moreno (35) in 1947 He found that the condition had a predilection for women was bilateral usually appeared in the spring or fall and was generally accompanied by eruptions on the lips and neck Some immediate but mainly delayed positive intradermal reactions were obtained with *Candida albicans* extract Neither passive transfer nor reagins could be demonstrated The original focus was often intestinal sometimes interdigital cutaneous lesions of the feet were the cause Desensitization with Candida extract proved successful in the treatment of the eczema Excessive doses of the extract cause exacerbations

Since monilial infection is a not uncommon complication of antibiotic therapy id reactions may occasionally first manifest themselves at such times Peck (36) has seen naso labial and eyelid eczema flare up in a patient with inguinal dermatitis following the use of tetracycline antibiotics In this instance the diagnosis was moniliasis engrafted on seborrhea The use of Nystatin has resulted in clearing of numerous resistant and baffling instances of such dermatitis

ECZEMA OF THE EYELIDS IN GENERALIZED DERMATOSES

In certain generalized dermatoses such as atopic dermatitis neurodermatitis psoriasis and especially seborrheic dermatitis a non specific type of eczema of the eyelids may occur The distinguishing feature of these cases is that while the eyelid may appear to be the only area of skin involved and the eye itself may show changes careful search will reveal diagnostic skin lesions elsewhere Treatment of this type of nonspecific eyelid eczema is gentle and soothing in order to alleviate the acute reaction that is present

Atopic Dermatitis and Neurodermatitis

Atopic dermatitis is believed to be an allergic dermatitis of internal origin The disease begins in the young as infantile eczema It is an extremely pruritic condition with a predilection for the eyelids (fig 81) the face the antecubital and popliteal flexures and the sides and back



Fig 81 Atopic dermatitis of the eyelids

of the neck The scratching induced by the intense itching is a major cause of aggravation and secondary infection of the eczema As the name indicates a familial history usually is obtained and other allergies such as hay fever and asthma are present or may supervene later The patient almost always exhibits multiple atopic sensitivities of the "immediate" type evidenced by immediately positive reactions to intracutaneous or scratch tests Most of the time however the agents responsible for the eczema are not demonstrable by these intradermal wheal tests Blood eosinophilia often is present The eczema is characterized by exacerbations and remissions over a period of years Such variations may depend on changes or modifications of the allergenic substances believed responsible especially foods Emotional and climatic as well as atmospheric factors seem to play a role Exacerbations are common in winter, yet in some patients they occur in warm weather

Atopic eczema responds to local steroids especially hydrocortisone but is most effectively treated symptomatically by systemic steroids or ACTH Antihistamines such as Benadryl may be helpful because of their antipruritic and sedative actions

The occurrence of cataracts as a complication is well known (chap 20) Hogan (37) has recently reported five cases of severe keratoconjunctivitis associated with atopic eczema, paralleling the skin activity and characterized by thickening and hyperemia of the conjunctiva and opacification and vascularization of the cornea Conjunctival eosinophilia

was noted Prompt improvement occurred with oral or topical cortisone therapy This subject is discussed in more detail in chapter 15

Neurodermatitis often without atopy occurs in adults and is usually related to one circumscribed area

Seborrheic Dermatitis and Psoriasis

Seborrheic dermatitis is a superficial scaling dermatitis of diffuse involvement rarely limited to the eyelids (fig 82) Typical sites of occurrence of the lesions are scalp (dandruff) eyebrows lid margins sternum and axillae and behind the ears Seborrheic blepharitis is characterized by greasy scales which reveal numerous yeasts (*Pityrosporum ovale*) on scrapings An associated conjunctivitis may be present but superficial epithelial keratitis only rarely occurs and is not likely to be confused with the staphylococcal variety Thygeson (32) has suggested that this keratitis represents an allergic response to *Pityrosporum ovale*

The dry skin of the eyelids of the seborrheic individual may serve as the predisposing factor in both allergic and infectious eczema

Psoriasis favors the hair line of the scalp elbows knees and extensor surfaces of the extremities The eyelids and face are rarely affected Plaque like hyperemic scaly lesions occur Ocular complications such as conjunctivitis and keratitis are unusual but may be severe when they occur



Fig 82 Seborrheic dermatitis of the eyelids (Theodore (1))

Treatment of Nonspecific Types of Eczema

The basic principle in the treatment of the acutely inflamed eyelid is a gentle, soothing stage-by-stage symptomatic approach. When edema and erythema are present astringents in the form of wet dressings are indicated. Camomile tea or cold milk are the mildest; dilute aluminum acetate (1:2) and two per cent sodium propionate are also useful. After the acute signs have subsided (in twenty-four to forty-eight hours), and the condition has become subacute, pastes are employed since the further application of compresses would lead to excessive dryness and consequent fissuring. A paste is a mixture of powder and grease. Lassar's zinc paste containing zinc oxide, talcum, lanolin, vaseline and wax, is the one most commonly used. A paste being porous because of the powder it contains will cool the skin and adsorb the microscopic ooze that exists at this subacute stage; an ointment being nonporous will heat the skin and is not well tolerated. The paste is applied in a very thin film morning and night. Soap and water should be strictly prohibited. If cleaning is desired gentle sponging with olive oil is indicated. After several days of application an excessive dryness may develop. At this stage when only minimal inflammatory signs are present, a mild ointment like petrolatum or boric acid ointment should be applied very thinly at night and almost but not quite removed with dry cotton in the morning.

Up to this point only bland medicaments are used. The use of pharmaceutically active drugs such as sulfur, mercury, tar and Vioform is reserved for chronic infiltrated cases. The drugs should be prescribed in weaker concentrations than those used routinely on the other parts of the body. If a seborrheic basis is suspected, one to two per cent sulfur may be given in an ointment base. If an atopic constitution exists, one to two per cent coal tar is indicated. Ammoniated mercury, one to two per cent, may be very effective in the seborrheic type or where psoriasis plays a role. Vioform, one to two per cent, has proved generally valuable in chronic eczema and is especially effective where the lesions have an impetiginous character.

Fissures which occur when the skin begins to dry should be cauterized with two per cent silver nitrate. Then the medication, paste or ointment, is applied directly to the cauterized fissure to counteract the extreme dryness of the caustic.

Many drugs such as tar, sulfur and Vioform are supplied in a vanishing cream base. Creams are thinner than ointments because of their greater fluid content. Vanishing creams are soaps, being oil-in-water emulsions in which the fats have been saponified by suitable alkalies. They have a cooling effect because they evaporate, yet they do not dry to excess since a film of bland fatty soap remains. Vanishing cream bases embody in

one preparation the three principles of treatment outlined above 1) moisture for the acute stage, 2) paste for the subacute stage, and 3) softening greases for the chronic stage Thus they may be substituted in subacute or chronic cases with a reasonable degree of success, but the stage by-stage approach described above is generally more advisable if the patient can be seen frequently enough

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14

AFFECTIONS OF THE LID MARGIN AND THEIR RELATION TO ALLERGY

At this point it might be useful to consider just how and to what extent certain common eyelid affections fit into the framework of allergy. While many authors have assumed that these entities may arise on an allergic basis especially from foods, it would appear that the role of allergy in the causation of conditions such as blepharitis, meibomitis, hordeolum and chalazion must be assessed with considerable caution. Since staphylococcal infection is so important in the etiology of the majority of such cases, and since this bacterium often evokes an allergic response which frequently dominates the picture to the extent of perpetuating the condition until the bacterial hypersensitivity is either alleviated or eliminated, one may suggest that in this sense at least, lid margin affections have an allergic aspect. Beyond this, however, it is difficult to make any affirmative statements regarding an allergic mechanism. It must be remembered that on many occasions neither bacterial infection nor bacterial allergy can be demonstrated and that often no definite cause is found.

BLEPHARITIS

By blepharitis we mean inflammation limited to the lid margins and the cilia associated with scales and crusts. The condition is most commonly caused by infection with toxigenic staphylococci, in which event hordeolum and ulcers of the lid margin are frequently encountered. The next most common form, the seborrheic variety, is associated with other manifestations of seborrheic [illegible]atitis and the presence of the yeast *Pityrosporum ovale* (1) [illegible]umbers as evidenced by epithelial

*

scrapings These two major types may occur together Rarely, other bacteria such as Streptococcus, *E coli* and *M lacunata* (*B morax-axenfeld*) are found to be causes of blepharitis

In our experience except for the microbiallergic factor occurring in the staphylococcal variety we have never encountered true blepharitis of proved allergic origin For clarity it should be emphasized that we are talking about blepharitis with its typical clinical picture The lid margin may well be the initial site of an allergic reaction to medicaments, such as ophthalmic ointments applied at this region However in such instances this is soon easily recognized as the adjacent skin rapidly becomes involved in the eczematous process and the full blown picture of allergic dermatoconjunctivitis results

Only a few authors have encountered cases apparently related to food allergy A clearcut instance of allergy to eggs causing recurrent blepharitis with eczema of the lids and accompanying conjunctivitis as well as at times a superficial keratitis was reported by Hansen (2) Repeated tests showed that the inflammation cleared on abstinence from eggs and reappeared on their ingestion Since blepharitis was only part of the allergic reaction which also involved the remainder of the eyelid skin the cornea and the conjunctiva this case may not actually fit into the category under discussion—that is allergic inflammation limited to the lid margins only (true discrete blepharitis)

Ruelemann (3) however believes that ulcerative blepharitis may often be due to food allergy citing the interesting case history of an individual who ate large quantities of oranges and tomatoes despite extreme sensitivity to both Within one week after elimination of these foods the blepharitis cleared up Bothman's (4) case is much less impressive His patient had chronic follicular conjunctivitis marginal blepharitis and recurring chalazia The offending agent was stated to be wheat Limiting (but not entirely eliminating) the intake of wheat led to recovery, with no recurrences in three years Other authors have stated that blepharitis is frequently an expression of allergy but give no evidence at all for their opinions

One is forced to the conclusion that were true blepharitis often allergic in origin one would encounter many more clearcut cases

HORDEOLUM

A hordeolum or stye is a suppurative process developing in one of the glands of Zeis the sebaceous glands associated with the cilia It occurs almost invariably as a staphylococcal infection On the rarest of occasions other organisms such as *E coli* and Streptococcus apparently may also cause hordeola In recurrent styes hypersensitivity to staphylococcal

products is the rule and as in staphylococcal blepharitis often requires specific treatment

A few authors have observed patients in whom hordeola developed on the basis of food allergy Ruedemann (3) reported such an occurrence in a boy who developed styes within forty eight hours after eating chocolate to which he was extremely sensitive In this patient moreover the ingestion of any food containing chocolate caused severe headache Another interesting example of such allergy was reported by Hughes (5) The patient suffered from recurrent styes for which all treatment including autogenous vaccine was unsuccessful After an interval of three years during which she was not under observation she returned At this time she stated that ever since she had stopped eating peanuts two and one half years previously she no longer had had styes She was convinced that whenever she ate peanuts hordeola would occur within a few days

The possibility occurs that when such food sensitivities as well as contact allergies occur rubbing and other irritation of the eyelid may bring on secondary infection of the damaged skin resulting in styes Multiple hordeola assuming almost alarming proportion complicated serious allergic dermatoconjunctivitis in a patient of ours so sensitive to Merthiolate that the small amount present in one drop of fluorescein preserved with that mercurial was responsible for a serious allergic reaction Yet it would appear unjustifiable to consider these hordeola as due to contact allergy

MEIBOMITIS AND CHALAZION

Inflammation of the tarsal or meibomian glands may be either diffuse (meibomitis) or localized to one or more glands (chalazion) In either event two factors appear to be of etiologic significance 1) a metabolic or secretory anomaly and 2) infection generally staphylococcal although occasionally due to other bacteria or fungi The clinical picture depends largely on the relative importance of these two factors in the individual case Where an altered physiology of the glands seems to be operative meibomitis or chalazion may occur as an essentially asymptomatic affection where infection predominates the entity assumes considerable importance either in itself or as a hidden focus for a more dramatic and persistent involvement of the structures of the outer eye

Despite its common occurrence the essential nature and pathogenesis of a chalazion has not been definitely established Pathologically it appears to be an inflammatory granuloma consisting of granulation tissue various types of leukocytes plasma and epithelioid cells but characterized mainly by its richness of giant cells Although retention of glandular secretion would seem to play a primary pathogenic role infection often appears to be of equal etiologic significance It is generally recognized that

where a suppurative infection of a meibomian gland occurs as for example in what is known as an internal hordeolum a staphylococcal infection is the basis for the process It is our experience that in the great majority of early chalazia not necessarily of an acute inflammatory nature culture of the expressed meibomian contents reveals numerous toxigenic staphylococci At other times only so-called nontoxigenic staphylococci or no bacteria at all are found on cultures

We ourselves have never encountered any unquestionable manifestation of allergy other than bacterial allergy, as a cause of chalazion It is our impression that many patients who tend to recurrent chalazia manifest high degrees of hypersensitivity to staphylococcal products In fact where cultures of the lid margin reveal significant numbers of toxigenic staphylococci in such patients careful if prolonged treatment of the associated meibomitis by means of expression and desensitization with staphylococcal toxoid and autogenous vaccine is exceedingly effective In those patients whose cultures are negative such treatment is often less valuable unless a very marked hypersensitivity to staphylococcus toxoid exists

There nevertheless remains a group of patients in whom as noted above staphylococcal allergy or infection appears to play little or no role Some seem entirely the result of physical agents We have treated several refrigeration mechanics who suffered accidental sulfur dioxide burns of their eyelids After the subsidence of the acute inflammatory symptoms multiple chalazia developed In one of these patients the same sequence of events occurred again at a later date when he was burned once more by sulfur dioxide

The role of food allergy in the causation of chalazia has been considered by some observers Bothman's patient with blepharitis and chalazia has already been mentioned One cannot pass judgment on the merits of his conclusions For what it is worth we are recording an experience of ours This patient an alert and extremely observant atopic individual insists that he develops chalazia only after the ingestion of nuts and ice cream His chalazia respond to expression of the lid margins when treated early enough and the expressed material is always sterile on bacterial culture Wolpaw (6) has observed a girl of 7 years allergic to eggs who on three occasions developed chalazia in all four eyelids within forty eight hours of egg ingestion

Lowenstein (7) has advanced the theory that autosensitization brought about by repeated resorption of the secretion of obstructed meibomian glands causes chalazia He feels that this material acts as an antigen Lowenstein's interest in this subject was based on the fact that repeated injections of horse serum into the eyelid tissues resulted in perivascular

(cellular) infiltrations very similar to those resulting from injections of tuberculin According to him chalazia arise through repeated resorption of desquamated glandular epithelium and in their histologic development show an allergic nodular character Löwenstein notes that the frequency of chalazia in rosacea of the skin of the lids is closely related with other possible allergic complications of rosacea

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15

ALLERGY OF THE CORNEA

A large part of corneal disease in the broad sense is allergic in nature. In fact almost all types of keratitis except the traumatic, infectious and dystrophic varieties appear to have an allergic facet. The cornea, therefore, manifests all recognized forms of allergic reactions including the atopic, microbial and contact types. Furthermore, other diseases which occur in allergic individuals, such as atopic dermatitis and possibly rosacea, demonstrate corneal lesions. There are no pathognomonic allergic inflammations of the cornea. Lesions vary greatly in intensity, site of involvement and morphologic appearance. Moreover, even recurrence of allergic reactions due to the same excitant may vary in each attack. These features of corneal allergy are what makes it so interesting and important in the differential diagnosis of diseases of the cornea. There is some evidence that the corneal healing process is influenced by allergic phenomena. The clouding of corneal grafts has been attributed on the one hand to the foreign corneal protein of the heterotransplant and on the other to microbial allergy. It is even possible that autogenous allergy may affect the healing of corneal wounds, both operative and traumatic.

Because of its transparency and its lack of blood vessels except at the limbus, the cornea offers unique advantages for the study of allergic phenomena. The largest part of the cornea, namely the parenchyma, is a collagenous stroma which is the ideal terrain for the allergic inflammatory reaction. The latter causes a fibrinoid degeneration of collagen tissue which is a characteristic feature of the allergic state—a fact which has been stressed by Klemperer (1). While fibrinoid degeneration alone is not equivalent to allergic tissue reactivity, it is nevertheless so suggestive of it that Klinge (2) based his concept of the allergic nature of rheumatic fever chiefly on this factor.

THE BASIS FOR THE ALLERGIC REACTION

A large part of the early experimental work in ocular allergy was performed with the cornea as shock organ especially with a view towards elucidating the pathogenesis of interstitial keratitis due to syphilis While the latter is hardly as important a disease as it used to be, nevertheless these corneal investigations enable us to understand better the role of allergy both in other affections of the cornea and in the remainder of the eye itself

In 1881 Loeffler (3) showed on the basis of animal experiments that the cornea can be protected against vaccination with the microorganisms of mouse septicemia by first immunizing the animals by means of intravenous injections of tiny doses of such microorganisms Loeffler's investigations indicated that the cornea participates in the general immunity of the entire animal and that under favorable conditions infections of the cornea could be successfully prevented by the production of such active immunity The fact that immune bodies produced in the organism and circulating in the blood stream are also present in the eye was conclusively established later by other investigators

When Richet and Portier (4) showed in 1902 that dogs injected at various intervals with extracts of medusae are much more sensitive to the second injection than the first the science of allergy was born They were the first to use the term anaphylaxis to describe the curious property possessed by certain poisons of augmenting instead of diminishing the sensibility of the organism to their repeated action

Ophthalmologic investigators were not slow to realize that these newly discovered concepts offered an explanation of certain ocular disorders Wessely (5) in 1911 was a pioneer in demonstrating that the cornea is capable of reacting anaphylactically to produce parenchymatous keratitis V Szily and Arisawa (6) further elaborated on this work

In the United States Derby and Walker (7) in 1913 called attention to the anaphylactic nature of interstitial keratitis Verhoeff (8) in 1908 advanced a similar explanation for this disease Apparently the first investigator in the United States to perform actual experimental work in the field of corneal allergy was Schoenberg (9), who used human serum and tuberculin as sensitizing agents

As early as 1909 Weekers (10) had produced phlyctenules in rabbits sensitized to bovine tuberculosis Over the following twenty years this work was confirmed and expanded by many investigators

Thus two of the most important corneal diseases of that era namely interstitial keratitis and phlyctenular ophthalmia were shown to have an allergic etiology

CLASSIFICATION

Like allergies of the conjunctiva, eyelids and other parts of the eye, the various manifestations of corneal allergy can best be understood when they are considered on the basis of the allergic mechanisms involved. In fact, this mechanistic approach has particular advantages in regard to the cornea because different types of allergy may give relatively similar clinical pictures and because the type of reaction depends to a great extent on the degree of hypersensitivity, time of exposure and other factors which alter the clinical picture. The classification of corneal allergy is presented in table 9.

It should be pointed out that under certain conditions certain types of antigens tend to cause specific types of corneal lesions. The spirochete of syphilis usually causes interstitial keratitis. The reaction to tuberculin is most commonly phlyctenular ophthalmia—although rarely it may cause a deeper type of keratitis resembling interstitial keratitis. Chronic staphylococcic infection often leads to the formation of marginal infiltrates and ulcers. On the other hand, different antigens and even different allergic reactions may cause similar clinical lesions. Thus atopic and contact allergic responses may result in superficial keratitis with relatively similar clinical pictures.

This chapter will consider all forms of allergic inflammations of the cornea except interstitial keratitis, phlyctenular ophthalmia and vernal catarrh.

TABLE 9

Classification of corneal allergy (11)

1. *Atopic allergy (immediate)*
   a. Topical allergens: superficial keratitis (rarely ulceration)
   b. Generalized allergy: superficial and marginal keratitis (rarely deep)
2. *Contact allergy (delayed)*
   a. Drugs: superficial keratitis, deep ulceration
   b. Other contactants: superficial keratitis, deep keratitis
3. *Microbial allergy*
   a. Lues, tubercle bacilli (other bacteria): interstitial keratitis
   b. Tubercle bacilli, staphylococci, other bacteria, coccidioidomycosis, nematodes: phlyctenular ophthalmia
   c. Staphylococci, bacillary dysentery: marginal infiltrates and ring ulcers
4. *Keratitis of possible allergic origin*
   a. Vernal catarrh
   b. Keratitis associated with atopic dermatitis
   c. Rosacea keratitis
   d. Keratitis nodosa
5. *Allergic reactions in corneal transplants*
   a. Interstitial keratitis

ATOPIC REACTIONS OF THE CORNEA

Atopic reactions of the cornea are most commonly caused by pollen allergy or by certain ingestants. As one would expect they are chiefly superficial in nature although occasionally deep keratitis does occur. It is our opinion that superficial keratitis due to atopy is much more common than the reports in the literature would seem to indicate. Because of the mildness of atopic corneal reactions most cases are not referred to the ophthalmologist. Others are missed by allergists who have no experience in use of the slit lamp. Also many atopic reactions are self limited or improve as a result of the treatment of general atopy.

Contact allergy of the cornea may produce a clinical picture similar to atopic allergy—namely superficial keratitis. This fact makes the differentiation between the two types extremely difficult without a clear cut history. The differential diagnosis may be further complicated by the fact that a certain fraction of an allergen may produce an atopic reaction while another fraction may produce a contact reaction. Thus it is important to ascertain the type of exposure in addition to the type of allergen.

In contact keratitis there is apt to be an associated contact dermatoconjunctivitis since both of these tissues are exposed at the same time as the cornea. Such associated findings are of great help in ascertaining the diagnosis. Atopic reactions of the cornea are less apt to be associated with conjunctival and lid allergy because the allergen reaches the eye via the blood stream in the case of ingestants and the cornea may be the most important or even the only shock tissue in the eye. With pollens and dusts the allergen is absorbed directly through the corneal and conjunctival epithelium and the skin of the lids is rarely involved. Finally, the atopic reaction is immediate while contact reactions occur one or two days after the contact has taken place. A deeper atopic corneal reaction especially from ingestants may occur occasionally with little or no superficial component. This lesion while somewhat similar to the interstitial keratitis of syphilis only milder in degree is entirely different from the rare deep lesion of contact keratitis because the latter is usually an extension of superficial corneal ulceration due to the contactant.

The earliest reference in the literature to what would seem to be atopic keratitis is a report by Stern (12) in 1897 of parenchymatous corneal changes associated with urticaria. He did not give the etiologic factor. Lohlein (13) reported a similar case in 1913. More recent authors have generally attempted whenever possible to identify the allergen thus enabling us to classify the corneal lesions in the literature more accurately. However recurrent paroxysmal edema of the cornea has been noted by a number of observers occurring as part of (or following) attacks of angioneurotic edema and urticaria. This has been called acute paroxysmal intra

ocular edema or Quincke's disease of the eye (14) On many occasions the entire anterior segment is involved with uveitis and even secondary glaucoma (see chap 19) Such reactions are believed to be allergic (atopic) in nature

The atopic reactions of the cornea have been divided for purposes of discussion into the two large categories 1) lesions caused by pollens and dusts, and 2) those due to ingestants

Corneal Reactions to Pollens and Dusts

While the conjunctiva is commonly affected by hay fever (chap 3) corneal involvement is much less frequent and occurs in more severe cases It is generally confined to superficial keratitis, with a few isolated areas which stain with fluorescein We have also noted mild keratitis in conjunctival tests utilizing pollen extract Lowenstein (15) also mentions corneal lesions in hay fever Such keratitis is often self-limited and responds readily to the same treatment as the conjunctivitis This mild lesion presents no problem either diagnostically or therapeutically and should give little cause for concern

An interesting case showing that pollen may cause a more severe form of keratitis has been described by Mauksch (16) It began as a superficial keratitis which recurred every year at the time of pollination of grasses The keratitis appeared in May and did not clear until October There was thin pannus at the lower border of the cornea somewhat similar to trachomatous pannus In addition to sensitivity to pollen extract the patient also had hypersensitivity to tuberculin After the patient was desensitized with pollen extract the corneal lesions did not recur even though they had previously reappeared every year for twelve years We believe that this lesion was a sensitivity to pollens alone without any relationship to a tuberculous process

An alternate explanation put forth by Mauksch is that the corneal disease was on a tuberculous basis with the pollen serving to give it the final impetus to eczematous keratitis This is difficult to believe because of the clinical picture the lesion and the lack of any resemblance to phlyctenular keratitis

The effect of atopy on tuberculous corneal disease has been emphasized by Verhoeff (17) and Tooker (18) The latter described two patients with interstitial keratitis in whom the ingestion of certain foods (e g egg milk potato oatmeal and pork) caused exacerbations of parenchymatous corneal lesions due to tuberculosis Both of these individuals were highly *allergic and suffered from many drug sensitivities On the other hand* it is possible that the corneal lesion was not really tubercular in nature but the end result of repeated allergenic insults

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An even more severe reaction to pollen was presented by Woods (19) in 1924. A farmhand who was sensitive to corn pollen was scratched on the cornea of his right eye by a blade of corn. The eye became intensely inflamed and there was a plaque of infiltration in the corneal stroma. Since the patient demonstrated extreme hypersensitivity to corn he was gradually desensitized with corn pollen, and the interstitial reaction gradually subsided. Noe (20) cited a similar case of keratitis after a corn stalk injury in a farmer. He had three subsequent attacks with dense corneal infiltrates related to working with corn. The patient showed marked sensitivity to corn smut.

Another rare occurrence is the corneal lesion due to dust. The individual must have a very high degree of hypersensitivity and perhaps the cornea must be a special shock tissue. Braley (21) has observed several cases of sudden edema of the cornea associated with allergic rhinitis. In one case in particular there was a concomitant severe allergic conjunctivitis. Although he could not determine the exciting allergen Braley suspected a dusting powder. With each attack of corneal edema the superficial epithelium would slough but would become normal again within twenty four to forty eight hours without treatment. After repeated attacks however deep vascularization did develop in the cornea. Parlato (22) has described the case of a thirty six year old nun who had suffered from recurrent attacks of relatively severe keratitis for seven years. These were apparently due to the use of orris root in sachets employed as a deodorant for silken church vestments. There were ulcers of the cornea extending into the parenchyma. hyperplastic changes of the conjunctiva and redness of the lid. When orris root powder was placed in the fellow eye there was a marked reaction and the cornea became edematous. In this patient an immediate form (atopic) of allergy occurred. Orris root may also cause delayed (contact) reactions (see fig 51)

Corneal Reactions to Ingestants

The other large group of atopic reactions are caused by ingestants. While probably fewer they generally are more severe than corneal allergies due to inhalants. Although ingestants may also induce superficial corneal lesion it is not surprising that the larger proportion are in the parenchyma leaving the epithelial layer relatively intact. Thus the conjunctiva is less apt to show a concomitant involvement. At times typical marginal infiltrates may occur usually without associated conjunctivitis (fig 83).

Among the corneal allergies to foods Dean Dean and McCutcheon (23) reported six patients who suffered f[...] a form of interstitial keratitis which cleared when the re ponsible [...] discontinued. These patients developed grayish opacities with [...] al stroma. Loops of scleral ve

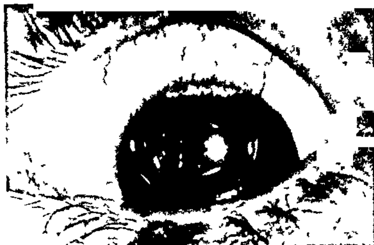


Fig. 53 Marginal keratitis apparently due to food allergy The offending allergen was probably shrimp

sels extended toward these lesions in a manner somewhat suggestive of syphilitic interstitial keratitis Also loops of conjunctival vessels extended into the cornea The characteristic salmon patch of interstitial keratitis of luetic origin however did not develop The appearance of this lesion was similar to the recurrent vascular keratitis of unknown origin described by Doggart (24) When all offending foods were removed from the diet the corneal lesions regressed Although the corneal stroma showed a tendency to become transparent again the vessels in the parenchyma continued to function for some time Among the offending foods as ascertained by history elimination diets and cutaneous tests were pork cottonseed meal wheat strawberries cucumbers cheese Coca Cola egg white chocolate and rye

Hansen (25) mentioned three cases of superficial keratitis due to foods T [illegible]

the cornea due to chocolate in the one case and a variety of nuts in the other

Lemoine (26) has reported dendritic like corneal ulcers due to hypersensitivity to chocolate but did not mention any extensive studies of his patients to prove that this food actually was the cause of the dendritic ulcer

Ingestants other than food may cause atopic lesions of the cornea al

though this is rare Of particular and almost unique interest is the case report by Sjogren (27) of a seventy five year old woman who developed corneal lesions after the ingestion of a powder *containing caffeine phenacetin* and antipyrine Even before the powder was swallowed the patient experienced a sensation all over her body including her eyes as if they were being stuck by pins and needles On the following day the conjunctiva and lower lids were red and there was slight pericorneal injection Small round opacities with very fine erosions and small subepithelial infiltrates developed in both corneas In the center of one cornea there was a large erosion *Corneal sensitivity remained normal throughout the attack On the third day striate keratitis was noted* The cause of this relatively severe atopic drug reaction was either phenacetin or antipyrine Sjogren suspects the latter because it is extremely allergenic and according to him antipyrine is responsible for skin changes in ten per cent of the people who ingest it

Reactions to Serum

Serum sickness may cause iridocyclitis retinitis and optic neuritis but seldom if ever *affects the* cornea *An unusual and atypical* example was described by Walker (28) The patient developed a severe keratitis two days following the intravenous injection of serum prepared from the patient s own blood which had caused an immediate anaphylactic reaction

CONTACT ALLERGY

The cornea is often involved in contact allergies of the eye Usually it is part of an allergic dermatoconjunctivitis so that the involvement of these tissues points *to the* correct diagnosis *Since the cornea may show only* mild superficial keratitis its involvement may be easily overlooked when the other parts of the eye have a more marked reaction In some instances the lid and conjunctiva are slightly affected but the keratitis is extremely severe On occasion the superficial cornea may show a similar picture to *atopic* allergic keratitis differential diagnosis will then depend on history and elimination of the offending allergen

In the usual case of contact keratitis there are associated signs of contact dermatitis As *described in chapter 5 the lids show swelling and redness* and the skin assumes an eczematous character The bulbar conjunctiva and fornices are often congested and the palpebral conjunctiva may *demonstrate* papillary hypertrophy All these as well as conjunctival eosinophilia are signs of allergic dermatoconjunctivitis

As one would expect with corneal involvement all of the symptoms of ocular discomfort become markedly aggravated Pain lacrimation and photophobia are the chief symptoms Both faint and dense superficial in

filtrates may occur any place on the cornea O'Brien and Allen (29) however stress a predilection for the limbal area The lesions need not stain with fluorescein if the process is essentially one of subepithelial necrosis Severe contact keratitis may extend into the deeper layers of the cornea Occasionally the middle layers of the corneal stroma are also involved in a necrotic process Moderate or severe iritis occasionally accompanies these lesions

Although conjunctival scrapings may not show eosinophilia early in the allergic episode diagnosis is not difficult when the keratitis is associated with allergic dermatitis and conjunctivitis Discovery of the allergen is often difficult but the diagnostic procedure is similar to that used for contact allergy elsewhere in the eye or body Careful history affords the best clue Patch tests utilizing the suspected antigen will aid in tracking down the cause Finally if there is still doubt a saline emulsion of the allergen can be instilled into the conjunctival sac in very high dilution

A variety of allergenic agents have been reported as the cause of this type of benign superficial keratitis O'Brien and Allen (29) have given an excellent description of the clinical findings and have reported five case histories in which the offending agents were orange peel Butyn hydrous wool fat used in the base for ophthalmic ointment a proprietary inhalant and fur

Six patients with painful red itching eyes were described by Annenberg (30) These irritated eyes had occurred following the cutting of weeds In two cases there were grayish areas of infiltration in the superficial layers of the cornea but corneal staining with fluorescein could not be elicited in any of the patients Apparently the chief allergen was the pollen of pigweed redroot (a type of ragweed) The cases described by Annenberg highlight the differences between the reactions to the different fractions of ragweed On the one hand hay fever is an atopic reaction to the protein fraction on the other superficial keratitis may represent a contact reaction due to the lipoid fraction As stressed previously in this book the differentiating test for atopic allergy is the immediate intradermal wheal and for contact allergy it is the positive patch test There is no relationship between the two types of reaction except that ragweed may cause both reactions in one particular patient thus complicating the diagnosis The cases reported by Annenberg were probably due to contact allergy because there was a delayed reaction the conjunctival and corneal lesions occurring two to four days after contact in one case there was an associated dermatitis probably contact in nature

Similar contact reactions causing superficial keratitis may be due to local anesthetics such as Pontocaine and Butyn Theodore (31) has reported a case of sensitivity to Larocaine A wide variety of drugs which are instilled

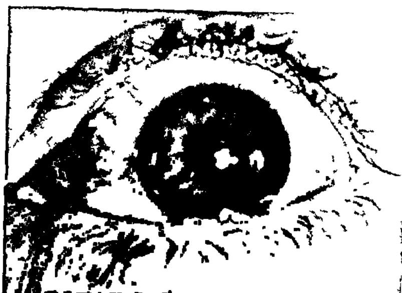


FIG 84 Superf c al keratitis due to contact allergy to sulfath azole o ntment Allerg c derm atoconjun t vitis w s present

into the conjunctival sac are capable of producing contact keratitis just as they can produce contact conjunctivitis but these instances are not re ported because the lesions are so mild and disappear almost immediately when the u e of the offending allergen is discontinued In addition to clin ically important allergic keratitis from the use of local anesthetics men tioned above we have encountered mild and severe corneal reactions from atropine scopolamine penicillin sulfonamides (fig 84) mercurials (fig 85) and quaternary ammonium compounds such as benzalkonium Waldbott (32) has described similar corneal involvement due to a hair net

Paraphenylenediamine and other related coal tar dyes are both highly allergenic as well as irritant and may cause disastrous corneal reactions Moran (33) reported very severe lesions due to hair dye containing para phenylenediamine In the right eye there was a hypopyon ulcer of the cor nea which perforated In the left eye the lesion was almost equally severe but the cornea did not perforate Ultimately secondary glaucoma devel oped When the inflammation finally subsided the left eye remained with vision of only 20/200 while that of the right eye was lost This patient showed a marked skin reaction to paraphenylenediamine More examples of aniline dye sensitivity are discussed in chapter 12

Taub Miller Fowler and Taub (34) reported on nineteen patients with superficial punctate keratitis due to allergy Many of the e patients suf



Fig 85 Superficial keratitis due to contact allergy to Merthiolate used as a preservative in fluorescein Allergic dermatoconjunctivitis was present

fered from both atopic and contact allergy. Others had only atopic allergy due to inhalants and ingestants. In most cases several allergens were mentioned and it is impossible to ascertain which offender actually caused the keratitis. The following allergens were among those listed by these authors: Butyn ophthalmic ointment, sulfathiazole ointment, dog hair, feathers, various foods (e.g. codfish, radishes, artichokes, etc.), ragweed and other pollens, orris root and pyrethrum. The only conclusion that can be drawn from this article is that a wide variety of inhalants, ingestants and contactants may be responsible for superficial punctate keratitis in sensitive individuals.

Treatment of Atopic and Contact Corneal Allergy

Treatment of these conditions of the cornea is not difficult in most instances because the affection is mild and subsides readily when the offending allergen is removed from the patient's environment. The local inflammatory process can readily be brought under control with local therapy of corticosteroids instilled at frequent intervals. In more severe cases atropine may be necessary and patching may be indicated for the treatment of a corneal ulcer. Secondary infection should be treated with local antibiotics but since the patient may be allergic to these drugs they should be used cautiously. Any associated iridocyclitis must be treated vigorously.

MICROBIALLERGIC KERATITIS

The allergic reaction of the cornea to products of bacteria protozoa fungi helminths and other similar protein products give a wide variety of corneal lesions which we have grouped together as microbiallergic reactions It is interesting that certain bacteria are associated with certain specific corneal changes Thus the classical picture of interstitial keratitis is *caused by the spirochete of syphilis and phlyctenular keratoconjunctivitis* is most commonly traceable to the products of the tubercle bacillus As mentioned previously these two forms of microbial allergy will be considered in chapters 16 and 17

The remaining microbiallergic lesions are 1) marginal infiltrates and ulcers and 2) disciform keratitis These conditions will be considered in this chapter

Marginal Infiltrates and Ulcers

Simple marginal or catarrhal ulcers and infiltrates are probably the most common manifestations of all corneal allergy (figs 86 and 87) The infiltrates are small lesions close to the limbus which break down and form ulcers crescentic with the limbus The size of these areas varies but occasionally the infiltrations are relatively large measuring as much as three to four millimeters in length and one to two millimeters in width These lesions may not stain at all or else take only a relatively faint stain with fluorescein as compared for example to the darkly green stain of a



Fig 86 Microbiallergic keratitis *marginal infiltrates in chronic staphylococcal infection*

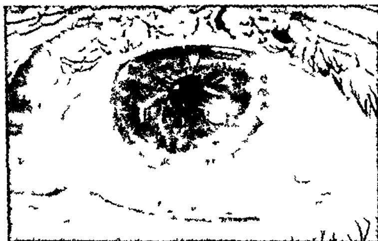


Fig 87 M rol llerg c kerat t s marg nal nfiltrate in pat ent w th cl ron c staphy lococcal blepl aro onj n t t s o curr ng as focal rea t on follow ng ntradermal n ject on of S apl ylo oc us toxo d Prompt respons to local l ydrocort one therapy

traumatic corneal abra ion Tl e conjunctiva adjacer t to tl e ulcer shows fairly marke l hyperemia (fig 88)

Tl e sudden occurrence of acute pain in a patient with cl ronic catarrl al conjunctivitis suggests the onset of a catarrhal ulcer However with ad



Fi 88 M ol all rg c kerat t s coales ng s er le marg nal nfiltrat s nula ng r ng ul er n pat ent w tl staphylococcal blepl aro onj nct tis

quate treatment, the infiltrates and ulcers remain superficial and tend to heal rapidly They often recur, especially in older individuals

In an excellent study of this lesion Thygeson (35) reported on one hundred and ninety-four cases of simple catarrhal ulcer One hundred and fifty-six cases were secondary to chronic catarrhal conjunctivitis twelve were secondary to acute catarrhal conjunctivitis, four were secondary to endogenous conjunctivitis, and eight were without any associated conjunctivitis Among the patients with chronic conjunctivitis *Staphylococcus aureus* was the responsible organism in one hundred and thirty three cases while the diplobacillus of Morax Axenfeld accounted for eleven cases In another eleven cases the conjunctiva showed normal flora One case of marginal ulcer was due to Pontocaine sensitivity, and another two cases were observed concomitant with vernal catarrh

Our own recent experience indicates that more marginal infiltrates and ulcers occur without associated conjunctivitis than these statistics reveal Perhaps such cases are due to other allergic phenomena rather than to microbiallergic reactions in conjunctivitis Instances of marginal lesions in atopic allergies such as foods have been noted The widespread use of antibacterial agents early in the course of conjunctivitis may be a factor in the changing statistical picture Contact allergy of the cornea as noted previously in this chapter often assumes a marginal pattern Here allergic dermatoconjunctivitis almost always occurs as part of the allergic reaction Keratoconjunctivitis due to contact allergy may at times be confused with marginal reactions in conjunctivitis due to bacterial allergy Conjunctival cultures and scrapings aid in the differentiation of these entities

While it has not been conclusively proven that marginal ulcers in bacterial conjunctivitis are allergic in nature the weight of evidence favors an allergic etiology especially as regards the Staphylococcus Here the antigen is probably the exotoxin of the bacterium Marginal ulcers caused by other bacteria such as the diplobacillus or *H conjunctividis* (Koch Weeks) may occur as a result of direct toxic action In favor of an allergic etiology for such infiltrates and ulcers are the following findings

1 Marginal ulcers rarely appear early in the course of Staphylococcus or diplobacillus conjunctivitis They occur commonly after the infection has been present for a period of time often after repeated exacerbations

2 The patients often show evidence of hypersensitivity to bacterial exotoxins in positive skin tests or may have foci of infection in sinuses and tonsils and other remote areas of the body However in some cases the skin tests are only slightly positive

3 It is difficult to isolate bacteria from scrapings of marginal ulcers

5 There are many similarities between marginal ulcers and phlyctenules, which are universally conceded to be allergic manifestations

6 As noted above, marginal ulcers have been observed in both atopic and contact allergies as well as vernal catarrh

7 Marginal ulcers in general respond very well to corticosteroids

Treatment In most instances marginal lesions of the cornea complicating conjunctivitis disappear promptly with adequate treatment of the conjunctiva Thus proper chemotherapeutic and antibiotic medicaments often are dramatically successful in clearing such marginal ulcers Corticosteroids the drugs of choice in marginal ulcers of non bacterial origin if necessary in microbiallergic marginal reactions should only be prescribed in combination with antibacterial agents indicated for the specific bacteria responsible for the basic conjunctivitis In general we decry such combinations for indiscriminate use in external ocular conditions especially in untrained hands Here we have a specific exceptional indication

With the means we now have available for treatment it is unnecessary and even harmful to use caustic agents or thermocautery in the management of these non infected corneal lesions Desensitization with Staphylococcus toxoid as described in the chapter on microbiallergic conjunctivitis is very helpful in recurrent cases associated with chronic and recurrent staphylococcal conjunctivitis

Ring Ulcers

Ring ulcers are marginal ulcers situated around the limbus in different areas which coalesce and cover a large part of the limbal area Conjunctival inflammation appears to be secondary not causative Although allergic in nature they have a somewhat different etiology from marginal ulcers Out of fourteen cases of ring ulcers Thygeson (35) found normal flora in twelve patients and coagulase positive *Staphylococcus aureus* in only two cases

The ring ulcers are probably a result of systemic microbial allergy Thygeson reports the history of a woman who developed bacillary dysentery in Puerto Rico One week after the onset of her bacillary infection she developed bilateral ring infiltrates With the aid of sulfonamides the dysentery was cured and the ocular lesions cleared simultaneously Five months later when the dysentery recurred the ring infiltrates returned again In another case reported by Thygeson the ring infiltrates were associated with periarteritis nodosa which was confirmed at autopsy The woman had bronchial asthma hay fever and other allergic manifestations She had conjunctival and blood eosinophilia Many authorities believe that periarteritis nodosa a collagen disease has an allergic basis

We have recently observed bilateral severe ring ulcers in a patient with normal bacterial flora and no clinical sign of infection throughout the body In another patient there was a severe ulcerative colitis Both patients re

sponded most dramatically to the local instillation of corticosteroids and although the lesions were so extensive at the onset they disappeared in several days

Treatment The treatment of ring ulcers is chiefly confined to the instillation of adequate concentrations of corticosteroids into the conjunctival sac at frequent intervals It is usually not necessary to augment this medication by systemic therapy If there is any question about the diagnosis a combined antibacterial and steroid therapy may be given It is important to rule out marginal herpetic ulcers which may simulate ring ulcers before prescribing steroids

Disciform Edema of the Corneal Stroma

Edematous reactions of the cornea of disciform character may arise in the course of various types of keratitis particularly herpetic or else may appear without any clearly demonstrable cause The tendency has arisen to group all such instances of corneal edema under the term disciform keratitis The disadvantage of considering all disciform stromal edema as one entity lies in the fact that whereas in herpetic keratitis corticosteroids are strongly contraindicated in other disciform lesions such therapy may be of value Beneficial effects in these cases may be due to a possible allergic component

Herpetic Keratitis

Except for primary infections due to herpes simplex the pattern of the disease is as follows *the virus appears to be dormant in the body* in seemingly harmless symbiosis but may be reactivated under varying trigger mechanisms such as fever trauma psychic disturbances menstruation sunburn and the administration of steroids Under such circumstances the classical picture of herpes simplex develops

The usual manifestation of invasion of the cornea by the virus of herpes simplex is the common dendritic ulcer The virus is often demonstrable in such cases This is essentially a superficial process usually responding to the removal of the virus by physical denudation of the infected epithelium usually with the use of iodine ether and other agents

In more long standing and persistent cases often when the *invasion* of the virus has been abetted by the injudicious use of *corticosteroids (fig*

stroma The

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aptly

described by Thygeson Kimura and Hogan (36) as the geographic map *ulcer (because its irregular outline resembles the map of a continent)* or the ameboid ulcer This lesion has an appearance very different from



FIG 89 Extensive superficial and deep keratitis due to herpes simplex precipitated by steroid therapy Patient had severe uveitis requiring intensive systemic and local corticosteroid therapy Typical dendritic keratitis ensued which despite iodine cauterization rapidly involved much of the corneal stroma assuming a disciform character However the corneal epithelium was only partially healed

the usual bacterial or traumatic corneal ulcer Another diagnostic aid that we have found useful in recognizing chronic dendritic ulcers is that somewhere along its margin a suggestion of dendritic erosion of the epithelium may still be recognizable on biomicroscopy This is particularly valuable in those ulcers where more rounded less ameboid extensions occur Such chronic herpetic ulcers appear to be essentially the result of infection even if the virus is not readily demonstrable (36) Treatment in such infections although difficult follows along the lines of the more superficial disease The remaining virus must be eliminated and any agents such as the steroids that activate the process are contraindicated Sometimes a conjunctival flap or keratoplasty is performed

The term metaherpetic keratitis has been used by many authors to describe chronic invasive herpetic keratitis In this discussion we agree with Thygeson Kimura and Hogan that the term should be avoided We feel that there is no uniformity as to its exact meaning if one is talking about a chronic herpetic ulcer one should so call it or if it is a disciform process it should be so designated "Metaherpetic" somehow conveys the impression that the process is different from herpes

There is still another type of keratitis that complicates the involvement of the cornea with the virus of herpes simplex disciform keratitis There

is some suggestive evidence that in certain lesions of this type an allergic mechanism may play an etiologic role. The trouble is that the term disciform keratitis as now used is too all inclusive, so that confusion arises *and management becomes difficult.*

Disciform lesions. Originally, disciform keratitis was meant to describe a disk like opacity situated in the corneal stroma which often assumed twice its usual thickness *in the involved area, and was associated with* descemetitis. Usually the corneal epithelium was relatively intact and staining with fluorescein revealed little or nothing. Most such cases were attributed to herpes simplex *infection on the basis of exposure to viral infections* (colds, herpes labialis) often in association with trauma, and it was hypothecated that the virus had somehow entered the stroma through the epithelium. Many times the so called point of entrance could not be demonstrated. Such cases were of themselves very serious; resultant central opacities, after the edema of the cornea had subsided, would reduce vision to the extent of industrial blindness. There seems no clear cut evidence other than circumstantial that the *condition is always due to herpes simplex.* Sometimes herpes zoster and vaccinia seem causative. In still other instances the cause is not demonstrable.

Braley (37) has been an important exponent of the allergic nature of disciform keratitis. We have summarized some of his major points: 1) the process appears to be a collagen reaction; 2) he has been unable to isolate herpes virus in disciform keratitis; 3) during the first few days of disciform keratitis there is a slight drop in the patient's serum antibody titer, but then there is a sharp rise, indicating that a state of hyperimmunity apparently exists; 4) *the presence of fixed tissue antibodies to* herpes simplex virus has been demonstrated (this fixed tissue immunity is closely related to hypersensitivity). Braley concludes that in disciform keratitis the herpes virus acting as an antigen combines with the local and

1) the
2) the

type occurring in association with demonstrable herpetic ulceration. It is hypothecated that in the first (classical) variety the cause has not been *demonstrated and may possibly be allergic in nature;* in the second form where a herpetic ulcer preexists, while allergy possibly operates in the production of the stromal edema, the infectious component of the process predominates to the extent that corticosteroids must not be used.

dendritic foci and show marked loss of corneal sensation. ...

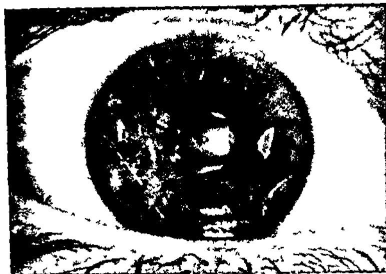


FIG 90 Disciform keratitis Here the epithelium was intact and characteristic central stromal edema with folds in Descemet's membrane were present Steroid therapy locally resulted in complete resolution of the keratitis

often appears to be evidence of an active or chronic herpetic infection with superficial ulceration in addition to the stromal edema On the other hand other forms of disciform keratitis are less intense more rounded have a practically intact corneal epithelium and corneal hypesthesia is less pronounced

The cautious use of corticosteroids with daily observation at the beginning of therapy should be tried in those instances of disciform keratitis where no herpetic component is demonstrable This in our experience has resulted in dramatic resolution of a process that may otherwise lead to permanent impairment of vision due to scarring However since the herpetic form of disciform keratitis is now unfortunately more common a thorough history and examination to rule out herpetic infection are mandatory before steroid therapy is instituted

OTHER KERATITIS IN ATOPIC INDIVIDUALS

The cornea is occasionally involved among the many manifestations of several generalized diseases of apparently allergic origin Chief among these are atopic dermatitis and periarteritis nodosa

Acne rosacea is a disease of unknown etiology involving the skin of the face Among the many factors which may affect the pathogenesis

of this condition such as hormones and vitamin deficiency, several authors believe that allergy is most important (38–40) The role of focal infection and the general allergic background of many patients with rosacea keratitis have been stressed by some investigators

The corneal lesions in vernal catarrh have been considered in chapter 8

Keratoconjunctivitis Associated with Atopic Dermatitis

Atopic dermatitis is characterized by thickening of the dermis scaling and pigmentation It is accompanied by severe pruritus which leads to secondary aggravation of the lesions due to scratching Characteristically the antecubital and popliteal areas the sides and back of the neck face head axillae, shoulders and thorax are affected but in severe cases the entire body may be involved This form of dermatitis occurs in atopic individuals Such persons have a hereditary tendency to develop allergic They probably become sensitized at birth and become affected with infantile eczema Later the sensitivity becomes multiple so that it is impossible either to desensitize these patients or to find any environment in which they can be free from antigenic factors Atopic dermatitis is usually accompanied by an elevated eosinophile count in the blood and body exudates A more extensive review of this disease is given in chapter 20

Hogan (41) was the first to describe an entity which he calls atopic keratoconjunctivitis a lesion occurring in persons suffering from atopic dermatitis *This condition complicates atopic dermatitis in the same* manner as does atopic cataract While the disease atopic dermatitis occurs in individuals who are subject to atopic allergies (the immediate type of the allergic reaction) the dermatitis is not a clear cut allergic response to a specific allergen Neither is the keratitis nor the cataract Thus while Hogan s choice of the term atopic keratoconjunctivitis is in line with the terms atopic dermatitis and atopic cataract it must be understood that it is a complication of the disease unfortunately named atopic dermatitis and not an atopic reaction of the cornea similar to those discussed earlier in this chapter

Hogan described five cases with this condition and deserves full credit for calling to the ophthalmologists attention this entity associated with atopic dermatitis The disease begins some time after the onset of the dermatitis as a bilateral conjunctivitis associated with a burning sensation and mucoid secretion The conjunctival inflammation may undergo exacerbations and remissions similar to those of the skin Secondary infection with bacteria when it occurs may complicate the picture

According to Hogan the corneal affection may occur simultaneously with repeated exacerbations of conjunctivitis or it may follow them The superficial third of the periphery of the cornea is affected first The corneal stroma near Bowman s membrane becomes clouded The lesion gradually

spreads deeper into the stroma and, after some time, blood vessels push in from the limbus The corneal epithelium over the area of keratitis becomes edematous and shows minute punctate staining with fluorescein (fig 91 and 92)

Over a period of years new areas of corneal involvement develop In

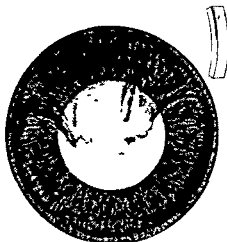




Fig 91 (*above*) Keratitis associated with atopic dermatitis (drawing) (courtesy of Dr M J Hogan)

Fig 92 (*below*) Keratoconjunctivitis associated with atopic dermatitis (courtesy of Dr M J Hogan)

Hogan's most advanced case the entire cornea became hazy and vascularized with resultant diminished visual acuity When the attacks are mild the disease remains confined to the periphery, but when the keratitis is more severe the lesion becomes more diffuse Secondary infections often occur and complicate the picture

Hogan lists five essential criteria in establishing a diagnosis 1) typical lesions of atopic dermatitis, 2) hereditary tendency, 3) frequent associated allergies such as hay fever rhinitis asthma and urticaria, 4) keratoconjunctivitis associated with skin exacerbations with vascularization of the stroma following each attack, 5) blood eosinophilia especially during the active phases of the disease, positive intracutaneous and skin tests to various allergens and negative patch tests

Two other types of corneal lesion have been described in association with atopic dermatitis Pillat (42) reported a case with superficial punctate keratitis Keratoconus is very rarely associated with atopic dermatitis *Four cases have been reported in the literature one case by Hilgartner* Hilgartner and Gilbert (43), two cases by Beretson and Baer (44), and one by McDannald (45) These cases had very severe and extensive atopic dermatitis with lichenification and pigmentation over the body, severe bronchial asthma and reactions to food and inhalant allergens Little attention has been paid to the association of keratoconus with atopic dermatitis It is possible that by carefully studying such cases ophthalmologists will gain better insight into the pathogenesis of keratoconus Keratoconus is also a complication of vernal catarrh

Steroid therapy both local and systemic, is the indicated form of treatment for the keratoconjunctivitis associated with atopic dermatiti

Rosacea Keratitis

Acne rosacea is a fairly common disease of the skin of the face It begins with episodes of vasodilation on the nose and cheeks At first these attacks are transient but later they become permanent Papules pustules and telangiectases develop The skin of the nose tends to hypertrophy with the formation of rhinophyma

The eye is commonly affected in this condition In almost every instance there is associated blepharitis often severe Our experience confirms that of Wise (46) this blepharitis is invariably associated with the presence of large numbers of pathogenic strains of *Staphylococcus aureus* The conjunctiva is diffusely hyperemic More rarely there may be small gray nodules on the bulbar conjunctiva near the limbus in the *interpalpebral* area These nodules resemble phlyctenules They ulcerate superficially and quickly disappear

Once rosacea extends to the cornea the patient's condition becomes

more serious The keratitis is usually bilateral with much vascularization it is difficult to treat and often leads to eventual loss of visual acuity

The corneal lesion begins with a small amount of vascular infiltration at the limbus an extension of rosacea conjunctivitis At first the vessels are small and show little branching In this region a gray area of well defined





Fig 93 (*above*) Acne rosacea
Fig 94 (*below*) Rosacea keratoconjunctivitis (same patient as fig 93)

superficial corneal infiltration develop giving the lesion a characteristic early picture somewhat similar to marginal ulcers In the next stage subepithelial infiltrates form in a typically triangular tonguelike shape and progress towards the center of the cornea The epithelium becomes eroded and a corneal ulcer develops At first the vessels associated with this lesion are anastamosing freely but later the vascularization becomes more fascicular Nevertheless it always remains superficial The corneal ulcers heal slowly and only with great difficulty they tend to break down again within a short time the infiltration pushing ever closer to the center of the cornea with resultant *impairment of vision Recurrent ulceration* and subepithelial infiltration give the corneal epithelium an irregular surface while thinning of the cornea leads to the formation of facets

The treatment of rosacea keratitis is difficult and usually only palliative *The staphylococcal infection should be controlled with antibacterial agents* toxoid injections and possibly autogenous vaccines The most valuable drugs for this disease are the corticosteroids both locally and systemically and ACTH in particularly resistant cases Atropine is necessary in more *severe cases We have had beneficial experiences in several particularly* severe cases with the judicious use of radiotherapy

Allergic phenomena The reader may perhaps wonder why the ocular complications of acne rosacea were included in this book While numerous etiologic factors such as hormonal disorders *vitamin deficiency and gas*trointestinal disturbances have been mentioned none of these has been proven to be the decisive factor An altered physiology must exist which causes vasodilatation in the facial area Three papers have expressed the belief that allergy plays an important role in this *alteration Two (38 39)* of these assumed that acne rosacea was probably due to bacterial allergy from a focal infection

Walker (47) on the other hand attempted to prove that rosacea keratoconjunctivitis is a true allergy She investigated seventy *six cases twenty* six patients had blepharitis or conjunctivitis without keratitis thirteen had their first attacks of keratitis thirty seven were recurrences Specific allergens were demonstrated in fifty two of the seventy six individuals tested Family history of allergy was *reported in fifty six instances* but allergens were found in only forty three of them The remaining nine patients who demonstrated specific allergens did not have any family history From these data Walker concluded that allergy was present in

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six weeks The twenty *four patients without demonstrable* [illegible]

given ten graded injections of nonspecific histamine azo globulin two injections a week for five weeks (0 05 0 1, 0 2 cc increasing by 0 1 cc up to 1 cc) In addition any secondary infection was treated with chemotherapy and Dithranol (dihydroxy anthranol) was applied to the skin for two weeks We have not been able to find in the literature any confirmation of Walker's results Consequently we must await further data before we can conclude that rosacea keratitis is an allergic phenomenon

Another approach to the allergic etiology of rosacea keratitis is that of Zondek Landau and Bromberg (48) These authors felt that patients with this disease have an allergy to their own hormones a so called endogenous endocrine allergy They found that such patients suffer from asthma angioneurotic edema urticaria and other allergic symptoms They detect endocrine allergy by an intracutaneous test utilizing reactivated steroid hormone dissolved in 0 1 cc of superficially purified olive oil In a study of six cases with rosacea keratitis all patients showed a strong hypersensitivity to testo terone They desensitized these patients with gradually increasing doses of testosterone in oil from 0 01 to 1 mg and implantation of 10 mg pellets of testosterone propionate In all cases they reported considerable improvement with disappearance of limbal and corneal vascular dilatation and marked improvement in the facial rosacea Subjective symptoms disappeared almost completely These investigators believe that other hormones may act as allergens in some cases

Keratitis in Periarteritis Nodosa

Periarteritis nodosa is a disease perhaps of allergic nature which will be considered in greater detail in the chapter on the retina because it probably affects the choroid and retina more frequently than any other part of the eye Wise (49) described corneal ulcers in two cases with this disease Although one of these cases had severe associated uveitis caused by periarteritis nodosa in the other an actual causal relationship between the corneal lesion and the general disease could not be verified in the absence of histologic examination In another case report (50) a girl with periarteritis nodosa developed a corneal ulcer associated with lagophthalmos However pathologic study did not demonstrate that this ulcer was due to a local focus of periarteritis nodosa

ALLERGIC REACTIONS ASSOCIATED WITH CORNEAL GRAFTS AND TRAUMA

The clouding of corneal grafts from the tenth day to the sixth week following keratoplasty has been the subject of considerable speculation and study Castroviejo (51) is of the impression that the corneal clouding is the result of uveitis an allergic response to foci of infection harbored in the

nose and throat Thus the nongranulomatous iridocyclitis precipitated by upper respiratory infections causes a toxic aqueous which leads to opacification of the graft He claims that removal of the focus by means of ethmoidectomy tonsillectomy etc sometimes leads to clearing of the graft

An alternate explanation is that this type of opacification of homotransplanted material is due to donor recipient sensitization Thus the recipient is sensitized by foreign protein in the transplant Klima (52) in 1949 attempted to prove this hypothesis He believed that the antigenic reactions of the cornea demonstrated by Wessely and others operate even when corneal protein is introduced in a manner similar to keratoplasty His basic technique was to use an extraction of crushed rabbit s cornea which was injected into the corneal stroma of the recipient rabbit Fourteen days later the same rabbit s cornea was injected again with refrigerated corneal extracts If a relatively severe interstitial keratitis developed it was considered a positive reaction

In one group of rabbits the corneal extract was injected between the lamellae of the fellow cornea of the same animal In seven such experiments there were negative results in every instance In a second group extracts of clear or opaque corneas were injected between the lamellae of the cornea of another rabbit and fourteen days later a similar injection was made using the same extract A positive result was obtained in eighteen out of forty five cases in this group In a third group an extract of a different donor s cornea was used in the first and second injections In this group there was only one mild positive reaction in seventeen experiments He utilized these data to explain the opacification of corneal grafts The lack of experimental reactions he observed when autogenous corneal extracts were used might explain the usual lack of opacities encountered in clinical autotransplants In his second group the fact that more than one third of his homocorneal extracts (from other rabbits) resulted in interstitial keratitis supports the concept that the cornea of the donor may act as an antigen and cause an allergic inflammatory reaction in homotransplants of the cornea

Maumenee (53) used a different approach to demonstrate that the recipient may become sensitized to donor material It had been noted that occasionally skin transplants would be destroyed Many investigations have proved that almost any tissue transplanted from one individual to another may be destroyed due to the sensitization of the recipient to the donor material Grafts between identical twins survive because of the biologic similarity between the tissues of the donor and recipient—the same reason for the success of autotransplants

Maumenee first performed keratoplasties in rabbits using a 4 5 mm

mechanical trephine and obtained completely clear grafts in fifty per cent of such homotransplants to normal rabbit corneas. Even when the transplant was slightly hazy or a small pannus was present the graft did not become grossly cloudy except in one of sixty cases. This is in contrast to human grafts where a fair number appear successful for the first two weeks only to become opaque later on.

Maumenee felt that rabbit cornea is not as responsive to donor recipient sensitization as human cornea. In order to heighten the allergic reaction he inserted a piece of skin 2.0 by 2.0 cm from the same donor into a pocket flap under the panniculus carnosus of the abdominal wall in various recipient rabbits at varying intervals both before and after keratoplasties. When the skin from the same donor was used as an antigenic supplement (two weeks after the keratoplasty) the corneal transplant in twenty eight out of thirty eyes became opaque within two to three weeks after the insertion of the skin. Clinical appearance of this opaque graft was similar to that of human keratoplasties. Histologically there was an inflammatory reaction similar to that which occurs in homogeneous skin grafts. Maumenee showed that the biologic individuality of a corneal transplant lasts for only six to eight weeks after corneal grafting because that is the survival period of the donor cells in the corneal graft. From these experimental data he concludes that donor recipient sensitization is one of the causes of opacification of keratoplastics occurring from the second to the sixth week following surgery. Further investigation with the use of cortisone while not conclusive indicated that this drug may be of some beneficial effect in preventing clouding of the cornea. Maumenee recommends the use of this drug for the first six weeks following surgery; after that time the graft assumes the individuality of the recipient and all the donor cells have disappeared (fig 95).

Aside from the effect of allergy on keratoplasties it has also been suggested that following trauma an autoanaphylactic reaction may be responsible for an ensuing interstitial keratitis (54). This assumption was based on two cases of keratitis occurring after discissions of secondary cataracts in patients with old corneal opacities.

Allergy to sutures. Excessive reactions from catgut are noted more frequently as a result of their increasing use. Since most of these occur to chromicized catgut it is our opinion that they are primarily irritative in character rather than allergic—although the latter does occur and we have observed several instances where the reaction appeared to be on an allergic basis. Since organic animal materials as well as chemicals are in the product reactions of all types may occur. Silk is in general more inert but there are reactions to the beeswax utilized to facilitate its use (55). Beeswax is an allergenic material and is responsible for contact



Fig 95 Herpes simplex keratitis of a corneal graft The patient had a successful keratoplasty performed 1½ years previously because of corneal opacification following disciform keratitis The present herpetic infection is explained by the fact that the donor material assumes the susceptibilities and characteristics of recipient tissue

reactions in cosmetics It is interesting that so few reactions appear to occur from the dyes in the sutures

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16

PHLYCTENULAR KERATOCONJUNCTIVITIS

Phlyctenular keratoconjunctivitis has always been one of the most important diseases in ophthalmology Its great frequency its predilection for children together with its often severe course resulting in serious permanent visual loss due to corneal opacification has impelled investigators beginning with Paul of Aegina in the second century A D to study this bizarre and fascinating entity There is now almost universal agreement that the disease occurs on the basis of endogenous microbial allergy

Since the most important allergen is tuberculoprotein the occurrence of phlyctenular disease has paralleled that of tuberculosis With the waning importance of the latter as to both incidence and severity now apparent in many parts of the world phlyctenulosis in general has become much less common and during the past few decades has had a much more benign clinical course Concomitant with the decreased incidence of hypersensitivity to tuberculoprotein attention became focussed on other bacterial products particularly staphylococcal as increasingly important etiologic factors in phlyctenular disease In addition on the basis of experimental work it appears that a wide variety of unrelated allergies other than microbial may play a role in its pathogenesis The fact that phlyctenular keratoconjunctivitis as encountered in the United States is no longer preponderantly a disease of children is probably related to these facts

Confusion has arisen at times because of the tendency of early investigators to use the term eczematous keratoconjunctivitis for the entity we are discussing As the indefiniteness of the term eczema would imply, this nomenclature had value during a period when the fine distinctions

in corneal and conjunctival diseases were not yet recognized. As the clinical picture and etiology of phlyctenular keratoconjunctivitis became better defined the term eczematous keratitis was gradually discarded.

CLINICAL PICTURE

Phlyctenular disease, which has a predilection for the limbus and thus classically involves both the cornea and conjunctiva, may, however, be limited to either of these two structures at relatively distant sites. Not only have phlyctenules been found in the bulbar conjunctiva away from the limbus, but Hselmuz (1) has reported lesions on the tarsal conjunctiva of patients with severe *diffuse conjunctival phlyctenulosis*, and Gutzeit (2) has noted small phlyctenules on the lid margins.

Phlyctenular Conjunctivitis

The conjunctival phlyctenule is a small yellowish nodule surrounded by injected conjunctival vessels although the lesion itself does not contain any vessels. It varies in size from almost pinpoint to several millimeters in diameter. The nodule may resorb within a short time or, on the other hand, it may develop into an ulcer which heals after several days. Although there are relatively minimal conjunctival changes, the patient has a certain amount of lacrimation and photophobia. True phlyctenules do not tend to extend like infectious processes, but neighboring phlyctenules may coalesce. Since phlyctenules often develop in undernourished children with poor resistance, it is not surprising that secondary infection, especially with staphylococci, often complicates phlyctenular conjunctivitis. When such mucopurulent conjunctivitis develops, the symptoms may reach a severity comparable to that described below in phlyctenular keratitis.

In miliary phlyctenular conjunctivitis the phlyctenules appear in large numbers and the whole limbal area may become covered with tiny nodules. They can either resolve or become confluent, forming a ring ulcer which may even jeopardize the nutrition of t[illegible] cornea.

According to Kruse (3) necro[illegible] [illegible]tenules occur [illegible] rare occasions when large lesions, inste[illegible] [illegible]ing become[illegible] Such formations may undermine the ad[illegible] [illegible] and heal w[illegible] [illegible] [illegible]tion

[illegible]hlycten[illegible]

Phlyctenular [illegible] uch m[illegible] its conj[illegible] part. The corne[illegible] a whi[illegible] ith wa[illegible] in the epithelial [illegible] mea[illegible] cloud[illegible] around the infi[illegible] mbi[illegible] o th[illegible] conjunctival ves[illegible] llen[illegible] th[illegible] phlyctenule show[illegible] r[illegible]

spread in both width and depth In severe cases the infiltrate can rapidly invade the deeper layers of the cornea and a crater like defect of the epithelial layer and Bowman's membrane results from suppuration and extensive necrosis This is the counterpart of the necrosing phlyctenule of the conjunctiva

In the absence of specific treatment, the course of these infiltrates varies greatly Mild phlyctenules remain only a short time and then resorb without leaving any opacity The more intensive and longer lasting processes which incite adjacent limbic inflammation generally lead to the development of phlyctenular pannus In this situation the superficial vessels from the limbus extend into the superficial corneal stroma under the epithelium towards the corneal infiltrate The pannus remains relatively thin While the trachomatous pannus is seen chiefly in the upper segment of the cornea the phlyctenular pannus occurs anywhere along the corneal periphery depending on the location of the phlyctenule In fact it may even surround the entire cornea Despite an initially stormy course the condition may heal with little or no residual corneal damage

Thygeson (4) differentiates five forms of phlyctenular keratoconjunctivitis 1) fascicular ulcer 2) marginal ulcer 3) miliary corneal infiltrates 4) diffuse central corneal infiltrates and 5) phlyctenular pannus

Fascicular ulcer This is the most characteristic form of the disease Here the greenish infiltrate at the limbus becomes slightly ulcerated and shows a tendency to wander towards the center of the cornea For this reason it has been referred to as wandering phlyctenule As it moves in a radial direction towards the center of the cornea the peripheral area of the phlyctenule heals but a group of vessels pushes forward from the limbus towards the phlyctenule—comparable to the tail of a comet These vessels pursue a direct radial course and do not develop a diffuse interlacing network This vascularization instead of being a healing process results in further corneal damage Riehm (5) has suggested that the vessels carry the antigenic tuberculin Thus the vessels bring with them material which sensitizes the superficial layers of the cornea The resulting superficial corneal lesion does not tend to ulcerate however should the fascicular keratitis run its natural course despite the gradual disappearance of the vessels a thick central opacity remains If however the fascicle of vessels is cauterized at the limbus the progress of the disease is arrested and the vascularization gradually resorbs

Marginal ulcers Marginal ulcers are probably abortive forms of the fascicular type and are situated perpendicular to the limbus rather than parallel like those catarrhal ulcers which on occasion occur as complications from secondary infection with staphylococci These have the typical appearance of marginal infiltrates

Miliary corneal phlyctenules These occur rarely and tend to cover extensive portions of the corneal surface

Diffuse central corneal infiltrates deep or superficial These lesions occur in long standing phlyctenular ophthalmia with many recurrences There are usually superficial or deep corneal vessels The extent of the process depends on the depth of the vessels and the distance from the limbus

Phlyctenular pannus This condition has been discussed above

PATHOLOGY

A conjunctival phlyctenule is composed essentially of epithelioid cells and occasional polymorphonuclear leukocytes surrounded by lymphocytes At times giant cells occur in small numbers Thus superficially the lesion may resemble that of a tubercle However both caseation and tubercle bacilli are absent As the lesion progresses the epithelium sloughs over the apex of the phlyctenule forming an ulcer which clinically stains with fluorescein In more severe cases the infiltration increases with the appearance of numerous mast cells and plasma cells Hemorrhages and tiny thromboses often are found Healing takes place by the growing in of granulation tissue and epithelium

The histopathology of the corneal phlyctenule is similar to that of the conjunctival lesion The purest form of this lesion is a round cell infiltration superficial to Bowman s membrane (6) When the corneal epithelium is thus raised in a sort of blister it bursts and a phlyctenular ulcer develops Schieck (7) explains this pathologic process by the fact that a *minute amount of specific antigen remains in the sensitized cornea and sets* off a purely local allergic reaction Isolated groups of round cells may appear under Bowman s membrane separating it from the superficial stroma As the round cell infiltration increases blood vessels invade this area and a phlyctenular pannus develops In less severe cases this may be located between the basal cells of the epithelium and Bowman s membrane in more severe cases the pannus is found between epithelium and the anterior lamellae of the substantia propria that is underneath Bowman s membrane or else involving it

DIFFERENTIAL DIAGNOSIS

The limbic manifestations of phlyctenular keratoconjunctivitis must be differentiated chiefly from the bulbar form of vernal conjunctivitis and less often from marginal corneal infiltrates The more severe and extensive corneal involvement characteristic of chronic phlyctenulosis may sometimes be confused with trachoma and rosacea keratitis Isolated phlyctens of the bulbar conjunctiva may rarely be confused with nodular episcleritis

Vernal conjunctivitis. If vegetations are present on the palpebral conjunctiva in conjunction with limbic vegetations the diagnosis of vernal catarrh presents no difficulties In the purely bulbar form of this disease the chief points differentiating it from phlyctenulosis are 1) bilaterality, 2) itching, 3) no ulceration of the proliferations and therefore no staining with fluorescein, and, 4) massive eosinophilia on epithelial scrapings It should be remembered that there is much more photophobia and inflammatory reaction in phlyctenulosis The phlyctenules stain with fluorescein because they tend to ulcerate Lastly, no conjunctival eosinophilia occurs

Marginal ulcers Marginal infiltrates may sometimes be present in association with limbic phlyctenules, especially in the nontuberculous forms and may also occur as a secondary complication of the tuberculous variety In uncomplicated instances of marginal ulcerations of the cornea one is not likely to confuse the two entities Phlyctenular involvement of the cornea is always accompanied by vascularization corneal blood vessels are absent even in extensive marginal infiltration

Trachoma. The manifestations of acute trachoma consist largely of severe papillary and follicular conjunctivitis involving the upper lid The corneal involvement begins at the superior limbus and the characteristic pannus is superficial to Bowman's membrane The inclusion bodies diagnostic of trachoma, are seen readily only in the early stage of active trachoma Whereas corticosteroids are beneficial in phlyctenulosis their use in trachoma may reactivate the process increase the number of inclusion bodies, and aggravate the entire picture

Rosacea keratoconjunctivitis The associated blepharoconjunctivitis as well as the dilated venules on the nose and cheeks generally suggest the diagnosis The corneal involvement of rosacea often has a tongue like parabolic configuration with its base at the lower limbus The thinner, finger-like, fascicular involvement of phlyctenular keratitis may originate from any part of the limbus but generally is found at its exposed portions Since pathogenic staphylococci are commonly found in the cultures of rosacea blepharoconjunctivitis and a high degree of hypersensitivity to staphylococcal products results phlyctenules may arise on this basis

ETIOLOGY

The etiology of phlyctenular keratoconjunctivitis has been the subject of numerous investigations Among these the most recent complete survey of this subject was written by Sorsby (8) His excellent paper delves into many facets of the etiology of phlyctenular ophthalmia and finally suggests a working hypothesis for the cause of the disease

Descriptions of nodules in the conjunctiva and cornea probably of phlyctenular nature may be found in the works of Paul of Aegina of ancient Greece, and of Ali ben Isa of the golden age of Arabian medicine

In more modern times St Yves in 1722 (9) and Wardrop (10) in 1808 have alluded to these nodules in the eye

With the advent of the bacterial era almost every type of microorganism was indicted as the cause of phlyctenular keratoconjunctivitis Very early, *Staphylococcus aureus* was considered the major etiologic agent before attention was focussed on the tubercle bacillus Concomitantly with this laboratory approach investigators were struck by the almost universal association of phlyctenulosis with other manifestations of a scrofulous diathesis The great amount of research work done in this regard clarified considerably the relationship of phlyctenular keratoconjunctivitis to tuberculosis as well as to other factors In fact while most cases are tuberculin positive a certain number of patients with phlyctenulosis are negative to tuberculin on skin test

Clinical observations of etiologic significance Although phlyctenular disease is believed to be a manifestation of allergy as will be detailed clinical studies indicate that a number of other factors may play a role in its pathogenesis Phlyctenular ophthalmia is essentially a disease of children and young adults However, there is no agreement among authors as to which age group is most commonly affected According to Krasso (11) the two peaks are between three to four years and at fifteen years Rolett (12) and Essen Moller (13) support these figures to some extent

Phlyctenulosis occurs more commonly in girls than in boys Carvill (14) reported 60 7 per cent and Weekers (15) reported 71 per cent of his cases among girls Several authors have noted a seasonal variation There is no agreement as to the time during the year of maximal occurrence January appears to be the month of greatest incidence for Graz April and May for Helsinki March for Greifswald and March to May for Vienna The smallest incidence appears to occur in November and December

Nonspecific factors such as nutritional deficiency pediculosis capitis focal sepsis and endocrine disturbances have been emphasized as etiologically important by clinical observers Of these it would seem to us that malnutrition vitamin A deficiency ariboflavinosis (16) and certain other factors associated with poverty such as overcrowding play a role in the development of that special type of allergic state necessary for the development of phlyctenulosis

Experimental etiologic studies At first it was thought that the phlyctenule might be the result of infection with tubercle bacilli However repeated attempts to produce tubercles by inoculation of phlyctenular material into the anterior chamber of rabbits failed to do so (17 18) Despite the fact that monkeys are extremely susceptible to infection with tubercle bacilli Wesely (19) failed on repeated occasions to produce disease in the conjunctiva of these animals with implants of material from phlyc

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Using rabbits already sen itized to bovine tuberculin Weekers (20) produced phlyctenules by instilling this antigen in the conjunctiva A histologic picture similar to that of the human variety was noted These results were confirmed by a number of other workers among these were Rubert (21) Stargardt (22) Gib on (23) Kuboki (24) and Kuniya (25)

That other antigens as well could produce phlyctenules in animals already sensitized to bovine tuberculin was demonstrated by Ro enhauch (26) U ing such sensitized rabbits he found that both living and dead staphylococci could produce a characteristic lesion These results were confirmed by others (24–28)

Further work on the pathogenesis of phlyctenules proved that this le ion could be produced not only in tuberculin sensitized eyes but al o in eyes sensitized to staphylococci (27) hor e serum (29) chemicals (such as tyramine) cocaine (27) and calcium casein ate (30) provided that once the eye had been sen itized the specific antigen was instilled again into the conjunctival sac

Riehm s (29 31 32) impres ive series of experiments in rabbits showed that the phlyctenule could be induced in the following ways 1) by utilizing hor e serum as both the sensitizing and the exciting agent 2) by sensitizing with horse serum and then using Staphylococcus products as the exciting agent 3) by causing recurrence (after a phlyctenule produced by hor e serum had subsided) on injecting more hor e serum intravenously and 4) by sensitizing a rabbit to horse serum by means of instillation into *one* eye only (phlyctenules may then be produced in *both* eyes following intravenous injection of the same antigen) Thus Riehm added considerable evidence to the theory that a phlyctenule is a nonspecific allergic reaction which can be induced in a variety of ways

In 1939 Katsnel on Kachan and Tufa (33) produced phlyctenules in rabbits sensitized to tuberculin by the introduction of sodium lactate into the stomach The possible relationship of these two antigens is further suggested by the fact that conversely according to the e workers the instillation of tuberculin into the conjunctival sacs of healthy non ensitized rabbits induced hyperlactemia

Phlyctenulosis of Tubercular Origin

Despite the fact that much of the newer experimental work indicates the often nonspecific character of the allergic reaction as ociated with phlyctenulosis on balance one fact stands out and cannot be ignored the relationship of phlyctenular disease to tuberculo is Although no viable bacilli have ever been isolated from phlyctenules and although the inoculation

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Phlyctenulosis of Tubercular Origin

Despite the fact that much of the newer experimental work indicates the often nonspecific character of the allergic reaction associated with phlyctenulosis on balance, one fact stands out and cannot be ignored the relationship of phlyctenular disease to tuberculosis Although no viable bacilli have ever been isolated from phlyctenules and although the inoculation



Fig 96 Phlyctenular keratoconjunctivitis in patient strongly positive to tuberculin Rapid cure with topical cortisone

of conjunctival tissue with viable bacilli causes an entirely different process the large mass of evidence points to an endogenous allergic reaction to tuberculoprotein

Woods in 1924 compiled from the literature 942 cases of phlyctenular disease (34) of which eighty five per cent were positive to tuberculin A more comprehensive analysis was made by Sorsby in 1942 utilizing 6150 cases from the literature (8) Excluding four reports totaling only 864 cases according to him no observer found less than seventy five per cent positive skin reactions to tuberculin In fact most of them found the incidence of positive reactions to be almost one hundred per cent In this material Sorsby found 960 cases of children under the age of six with positive reactions to tuberculin of these 78 3 per cent had phlyctenulosis

Realizing the pitfalls inherent in drawing conclusions from the results of tuberculin testing alone many investigators have attempted to correlate the incidence of phlyctenulosis with actual tuberculosis On the basis of family history radiologic evidence and clinical findings it appears rather definite that such a relationship exists Of 369 cases of phlyctenular disease studied by Ajo (35) the cause of death in the 55 that died was tuberculous in 35 instances In another series of 150 cases (36) of phlyctenulosis in children seventy four per cent under four years fifty per cent between four and seven years and thirty two per cent between seven and thirteen years had active tuberculous lesions Fritz Thygeson and Dur

ham (37) examined 346 children of Alaskan Eskimos and Indians who have a high incidence of tuberculous disease. They found 10 children with active phlyctenular disease and 143 children with evidence of old phlyctenular disease.

In general, throughout the world the incidence of phlyctenular ophthalmia has steadily declined during the present century. This trend was reversed, however, by the exigencies of war. During World War I and the immediate post-war years in Finland this decline stopped; in Austria and in the Netherlands an actual increase occurred. Similar experiences have been noted as a result of World War II. It is most probable that the decreasing incidence of phlyctenular ophthalmia is the result of the decline in both incidence and severity of tuberculosis throughout the world.

The studies of phlyctenulosis precipitated by the Calmette and Wolf Eisner reactions are an interesting approach to the etiology of the phlycten. The instillation of tuberculin into the eyes of patients who are sensitive to tuberculin had led to the development of cases of keratoconjunctivitis similar to phlyctenular ophthalmia. At the end of the last century massive subcutaneous doses of tuberculin were used in the treatment of tuberculosis and the rather common appearance of phlyctens in such cases was noted in the literature (38–40). Even as late as 1951 Damato (41) reported 10 cases of phlyctenular keratoconjunctivitis which followed inoculation with BCG vaccine. The phlyctens were usually single and limbal. Thus, with the more widespread use of BCG vaccine to confer immunity to tuberculosis, an increased incidence of phlyctenulosis may develop in its wake. However, since these cases are not severe, they should not serve as a contraindication to the use of the vaccine and will probably respond to local corticosteroid.

For many years, on a clinical basis, observers have noted that among the many factors triggering the endogenous allergy to tuberculin responsible for the phlyctenule, superimposed or associated infections with other organisms, such as the Staphylococcus, were of considerable importance. Thus, for example, the control of associated blepharitis is of itself beneficial in the therapy of phlyctenulosis, possibly by diminishing the local exposure of the blood stream to tuberculous antigen. Bjorkenheim (42) attempted to evaluate the significance of these secondary infections. She studied the antistreptolysin titer (AST) and antistaphylolysin titer (ASTA) in the sera of patients with phlyctenular disease in order to determine the role played by β hemolytic Streptococcus and *Staphylococcus aureus* infection in this disease. In active tuberculosis, according to various authors quoted by Bjorkenheim, there is a significant rise in the AST and ASTA in a high percentage of cases, and she therefore believes that β hemolytic streptococci and golden staphylococci have a significant influence on the tuberculous process in these patients.

In her own study of 250 cases of phlyctenular ophthalmia, Bjorkenheim found the AST elevated in seventy one per cent as compared with eighteen per cent in a normal Finnish series and seventeen per cent in her control group The presence of *Staphylococcus aureus* was noted by a rise in the ASTA in forty-three per cent of the patients with phlyctenular disease as compared with twenty-two per cent in the control group The beneficial effect of penicillin in this disease has been pointed out by Busacca (43) as evidence that bacteria which are controlled by penicillin play a role in the etiology of phlyctenulosis Bjorkenheim feels that besides tuberculosis a streptococcal infection and less frequently a staphylococcal infection alone or a mixed streptococcal and staphylococcal infection, also play a part in the genesis of phlyctenular disease In general the eruption of the phlycten appears to result from a streptococcal infection in tuberculous individuals

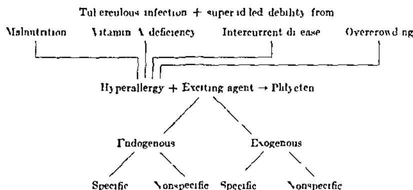
In view of these ideas one may speculate on whether in the presence of hypersensitivity to tuberculin an intercurrent infection caused by streptococci or staphylococci with the development of allergic reactions to their toxins may not have an additive effect on the original tuberculin allergy and cause the eruption of the phlyctenule This would be similar to the development of food allergies during the hay fever season in a patient with latent tendencies to allergic reactions to food Even bacteria with low antigenicity may initiate phlyctenular reactions Thygeson (4) points out that when phlyctenules occur in children during epidemics of keratoconjunctivitis due to Koch Weeks bacilli or pneumococci these bacteria act only as trigger mechanisms because of their low antigenicity They cause dilatation of limbal vessels during the infective process thus enabling more tuberculoprotein than usual to reach previously sensitized areas in the cornea

The exact allergic mechanisms in the production of phlyctenular keratoconjunctivitis have not been completely elucidated There are several opinions as to the mechanism involved Woods (34) has succinctly put forth his hypothesis by assuming a special sensitivity of ocular tissues to tuberculoprotein Thus a person who has a minute focus of tuberculosis in his eye develops a hypersensitivity in his ocular tissues Any further change in the hypersensitive state to tuberculin would lead to the development of phlyctenules

Sorsby (8) points to the fact that phlyctenulosis is an expression of what he calls hyperallergy Poverty, malnutrition and overcrowding may be responsible to some extent for the development of the necessary amount of hyperallergy to allow for the appearance of the phlyctenule If one assumes that only the specific antigen will precipitate the phlycten then there must be a liberation of tubercle bacilli or their products within the

patient s body to incite the phlycten If nonspecific irritants or agents are capable of causing the formation of phlyctenules then any number of them may be responsible for precipitating phlyctenular keratoconjunctivitis Sorsby has published a diagram which he believes is an indication of the likely mechanism in the production of phlyctenulosis (see diagram 1)

DIAGRAM 1



Moro and Keller (44) Lowenstein (45) and Riehm (46) all agree with the hypothesis that the basic sensitivity is to the tubercle bacillus and its products but that the phlyctenular reaction is nonspecific and therefore para allergic in nature Several types of trauma as well as infection can precipitate the phlyctenular reaction in tuberculin sensitive individuals There are many other influences such as chemical thermal hormonal and psychic stimuli For example measles can increase the sensitivity to tuberculin in children who are already tuberculin positive and even in tuberculin negative children one may occasionally obtain a positive reaction to tuberculin at the height of a vaccination reaction Marchesani (47) believed that chronically recurrent tuberculous inflammatory reactions of the eye are precipitated and maintained by focal nontuberculous infections Thus he also believed that tuberculosis plays a role in the etiology as a para allergy

Phlyctenulosis of Nontubercular Origin

It is apparent that most patients suffering from phlyctenulosis have positive reactions to tuberculin However since so many persons with positive tuberculin reactions have neither active tuberculosis nor phlyctenular disease the presence of a positive tuberculin reaction in a patient with phlyctenulosis does not of itself prove the tuberculous nature of the allergy Moreover a number of cases of phlyctenular disease have been ob

served where the tuberculin reaction was negative or where factors other than tuberculosis were definitely responsible for the allergic phlyctenular reaction

In the earlier literature there are reports indicating that nontuberculous phlyctenular disease occurred even at the time when the importance of tuberculosis as an etiologic factor was first emphasized Unfortunately most of these cases were not investigated extensively enough to rule out tuberculosis beyond the shadow of a doubt Heerfordt (48) described phlyctenulosis in patients with metastatic endogenous gonococcal conjunctivitis Peters (49) reported a case secondary to diplobacillus infection Schelbe (50) noted conjunctival phlyctenules after the injection of diphtheria antitoxin Moro (51) believed pediculosis to be the cause of the conjunctival lesion Kleinschmidt (52) found three out of five patients with phlyctenular conjunctivitis to have negative tuberculin tests

In more recent reports there are several careful studies in which tuberculosis was definitely ruled out During the course of a single year Wise (40) observed three cases between seven and ten years of age with negative intracutaneous reactions to tuberculin in concentrations as high as 1 10 Goldstein and Wood (53) in a study of seventy one patients with phlyctenular conjunctivitis found two children with negative tuberculin reactions One of these however had a mother with open pulmonary tuberculosis and the authors believe that if they had used higher concentrations of tuberculin this patient would have demonstrated a positive reaction In the other case the possibility of tuberculosis was definitely ruled out and a negative reaction was obtained to the intradermal tuberculin test (0 1 mg) Sime (54) on the other hand found a much higher percentage of cases with negative tuberculin reactions Out of one hundred and forty cases of phlyctenulosis seventeen or twelve per cent had no relation to tuberculosis Tuberculin tests were carried out using high concentrations and the possibility of severe anergising tuberculosis infections immediately prior to the test causing negative reactions was ruled out Ajo and Vare (55) also reported a similar case Bjorkenheim reported four cases of phlyctenulosis in children with negative tuberculin reactions but she does not give the etiology However one of these was vaccinated with BCG one day before the appearance of the phlycten so that tuberculosis might still have played a role in the etiology in this instance We have observed phlyctenular disease in a patient who had been paralyzed many years previously by poliomyelitis The tuberculin test was negative She had a large corneal phlycten which responded extremely well to topical cortisone We were unable to discover the cause of the disease In another instance in a well developed and well nourished medical student it was also impossible to discover the etiologic factor

In a number of instances, however, the responsible agent for nontuberculous phlyctenular disease has been determined. *Staphylococcus aureus* has been isolated as the cause of phlyctenular ophthalmia in a number of cases. Cerza (56) reported twenty-one cases with phlyctenules among infants during an epidemic of impetigo. Of the nine cases reported by Thygeson (57) in tuberculin-negative individuals, five showed a high degree of sensitivity to Staphylococcus toxoid. So sensitive were these children that even small doses of toxoid produced malaise and aching of the extremities. Such experiences underline the need for great care in desensitizing such patients. Thygeson stresses the fact that patients with staphylococcal phlyctenulosis have a much greater sensitivity to toxoid than do patients with other infections due to staphylococci such as blepharoconjunctivitis. Our experience is similar (fig. 97).

Another two of Thygeson's patients were children who lived in the San Joaquin Valley and gave positive reactions to coccidioidin. These children had recurrent limbal phlyctenulosis with little corneal involvement. Of his remaining two patients, one was probably due to moniliasis and the other had systemic lymphogranuloma venereum.

Other reports in the literature include the case of Schieck (58), whose patient had metastatic gonococcal conjunctivitis, and that of Chams (59), which was associated with leishmaniasis keratitis. Trypanosomiasis has



Fig. 9[illegible]. Phlyctenular keratoconjunctivitis [illegible] with [illegible] largest [illegible] phlyctenules [illegible] Extreme [illegible] to [illegible] Staphylococcus toxoid injection occurred with systemic symptoms. Dramatic [illegible] response to local steroids.

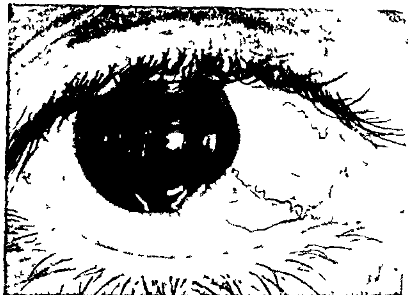


FIG 98 Phlyctenular keratoconjunctivitis complicating ulcerative colitis Excellent result with topical hydrocortisone

also been complicated by phlyctenulosis We have observed phlyctenular keratoconjunctivitis in association with ulcerative colitis (fig 98) Dramatic recovery was obtained with local cortisone

Laurell (60) believed that phlyctenular ophthalmia may be due in many instances to helminthiasis especially ascariasis and oxyuriasis In a case of ascariasis diagnosed by x ray the patient demonstrated the clinical picture of phlyctenular conjunctivitis Laurell also suggested that tuberculosis as well as helminthiasis can supply the antigen for this disease More recently Jeffery (61) reported two cases of phlyctenulosis due to nematode infestation in India and stated her belief that phlyctenular disease was a common ocular complication of nematode infestation and amebiasis in Nilgiri South India These organisms probably play a large role in the pathogenesis of the phlyctenule of tropical countries It is questionable whether this disease is indeed pathologically different from phlyctenulosis of western countries The tropical variety occurs more often in adults and tends to heal rapidly when the infestation is under control Since the exact nature of the tropical phlyctenule is not definitely known we should withhold final judgement on its pathology and pathogenesis until more data are available Thygeson (4) believes that phlyctenular ophthalmia is always due to bacterial allergy and never is a result of allergy to non bacterial proteins *e g* hay fever or urticaria He has never observed the development of phlyctenules in vernal catarrh or simple allergic con

junctivitis Especially significant is the fact, that in phlyctenular ophthalmia there is no conjunctival eosinophilia—such a constant feature of non bacterial allergies

TREATMENT

Prior to the introduction of antibiotics, ACTH and the steroids, the treatment of phlyctenular ophthalmia was difficult indeed as it was strictly nonspecific except for tuberculin therapy The results of treatment at that time were largely dependent on the initial severity of the lesion From a theoretical point of view, specific desensitization with tuberculin should be effective in the treatment of phlyctenulosis and especially in the prevention of recurrences It is difficult to evaluate the effectiveness of this medium of treatment because of the long period required for desensitization to become established the possible effect of such agents as riboflavin that may be present in the product used for this purpose and the value of general supportive therapy in building up the patient's resistance Furthermore, it appears that its use before the steroid era for phlyctenulosis was less universal than similar treatment for uveitis However where increased sensitivity to staphylococcal products appears to be the sole etiologic factor, desensitization with staphylococcal toxoid and vaccines is indicated to prevent recurrences

The value of adequate diet in the control and treatment of phlyctenular ophthalmia is still an open question Both Sorsby and Thygeson believe that nutritional deficiencies are not a direct causative factor but that they do have an indirect effect at least in relation to the tuberculous process Thygeson relates that he has seen many cases where attacks of phlyctenulosis ceased under adequate diet in the hospital only to return again when the children returned to their home environments and received neither sufficient nor proper food

The value of polyvitamin therapy in general as a dietary adjuvant is self evident Specific treatment with riboflavin and vitamin A have been stressed by some The evidence for such specificity is not impressive

The importance of the control of associated infections has been indicated previously In our experience this has been limited essentially to staphylococcal infection of the eyelids and conjunctiva To this end antitonsils seemed of value in previous decades This form of therapy may still be useful in certain resistant cases The cure of intestinal disease such as helminthiasis and ulcerative colitis may likewise be of considerable help in the management of phlyctenulosis

The introduction of corticosteroids has revolutionized the treatment of

phlyctenulosis We personally have experience with topical cortisone and hydrocortisone but believe that some of the newer cortisone derivatives should be equally effective In 1951, Thygeson and Fritz (62) reported excellent results with topical and systemic cortisone therapy in fourteen cases of phlyctenular keratoconjunctivitis In our experience as well as the experiences of others the local use of hydrocortisone has proved sufficient to control the large majority of cases so that systemic steroids which may be medically contraindicated, are unnecessary

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INTERSTITIAL KERATITIS

Interstitial disease of the cornea appears in large measure to be allergic in nature most instances are manifestations of microbial allergy more rarely atopic reactions are responsible What is known as interstitial or parenchymatous keratitis would seem to be best considered from this point of view An allergic concept is particularly applicable to the two major types of interstitial keratitis encountered clinically namely that due to lues and that due to tuberculosis In parenchymatous disease of the cornea ocurring in leprosy and trypanosomiasis actual invasion by the microorganisms appears to play a major role In view of the fact that microbial allergy is so important in other ocular manifestations of trypanosomiasis (1) it is possible that this rare interstitial keratitis may be allergic in nature The exact definition of what constitutes interstitial keratitis is vague and in one sense might include reactions following virus infections as well as trauma These are not considered here Interstitial involvement of the cornea due to atopy has been discussed previously

Since interstitial keratitis is most commonly caused by syphilis it has lost a great deal of its importance in recent years with the decline in incidence and better control of lues due to effective public health measures chemotherapy and now antibiotics Nevertheless a study of luetic interstitial keratitis offers valuable insight into the reactions of the cornea to allergic insults From the beginning it was apparent that luetic interstitial keratitis was different from other manifestations of syphilis and these differences can best be explained if we consider the disease allergic in origin Specific treatment usually is ineffectual indeed at times it aggravates the condition The best results even before the advent of corticosteroids were obtained with nonspecific measures such as fever

therapy The rare onset of interstitial keratitis following Jarisch Herxheimer reactions during the course of therapy with arsenicals further emphasizes the allergic nature of the disease (2) Lastly, a lesion identical in essential details to the disease process has been produced experimentally, utilizing allergic techniques

However intriguing the possibility of allergy in tuberculous interstitial keratitis is, the condition appears to be so rare, and so little definitive investigation in this direction has been done, that one can only speculate in this regard It must be observed that it is surprising considering the vast amount of experimentation in phlyctenulosis, using the cornea as a shock organ for tuberculous antigens, that no mention is made of the occurrence of interstitial keratitis It is of course possible that atypical corneal involvement in phlyctenulosis may be similar to tuberculous interstitial keratitis In support of this idea it is interesting to note that luetic interstitial keratitis on rare occasions, may assume a phlyctenular character Allergic reactions of the cornea due to tuberculoprotein have been discussed in the previous chapter

SYPHILITIC INTERSTITIAL KERATITIS

Clinical Picture

Interstitial keratitis occurs most commonly in patients between five and twenty years of age Two thirds of all cases begin during these years (3) The earliest symptoms are pain, lacrimation photophobia and spasm of the lids

The first sign of interstitial keratitis is edema of the corneal endothelium, *which may be demonstrated with the slit lamp* as much as several weeks prior to the appearance of circumcorneal injection Shortly thereafter a diffuse corneal haze is noted, it is due largely to epithelial edema which imparts the dull, lusterless appearance The stroma becomes translucent because of extensive cellular invasion forming spotty opacities which are at first faint and soft-edged but later conglomerate These cellular elements originate from the limbal vessels From the beginning iridocyclitis plays a major role in the clinical process While at first mild when full blown the picture includes striate keratitis with wrinkling of Descemet's membrane, and all the other signs of severe acute anterior uveitis

In the second or vascular stage, blood vessels invade the cornea from all sides, if the opacity is central When the opacity is more peripheral the vessels appear in the corresponding sector Those vessels which arise from the terminal arches of the conjunctival circulation advance a short distance over the surface and form a crescentic swelling or "epaulet" The deeper ones extend from the anterior ciliary vessels and invade the posterior por-

tion of the cornea in long parallel brush like lines They may pass across the diameter of the cornea and unite with brushes from the other side The deeper the vessels are situated the less they may be recognized individually on gross examination The blurred pale pink appearance of such vascularization led Hutchinson to call them salmon patches It usually takes about four to five weeks for such deep vascular invasion to develop In severe cases at the height of corneal invasion the cornea is thickened and intensely red The center of the cornea may become densely opaque with an uneven surface and a dirty grayish white color At times the vascularization becomes so severe and extensive that it is difficult to distinguish cornea from sclera

At this point at the height of this intense reaction when the case seems most hopeless a sudden change occurs and within a remarkably short time the inflammation subsides The signs of irritation fade the vessels shrink almost completely and the cornea takes on a more normal appearance It is in this stage of retrogression that the brushlike character of the vessels can best be observed In general the maze of capillaries shrinks away but in the process individual ones hypertrophy forming single large trunks This resembles the reestablishment of collateral circulation in an extremity

Experiments have shown that after section of the long ciliary arteries or ligature of the vorticose veins there is a whitish corneal opacity followed by dense invasion of vessels This sequence of events is suggestive of the evolution of the picture of interstitial keratitis The vessels which have formed in the cornea persist throughout the patient's life and although they do not carry blood can be visualized in the cornea as very fine threads Their characteristic appearance remains as telltale evidence so that many years later one can easily recognize the previous existence of congenital lues The cornea while thinned has many permanent opacities which often seriously impair vision Oksala (4) has given a comprehensive review of the corneal damage which remains long after the keratitis has subsided

The anterior uveitis may be difficult to diagnose because of dense corneal opacification during the disease Nevertheless if it is not treated the patient will be left with seclusion of the pupil which will become apparent only when the cornea clears

Aside from the typical course of interstitial keratitis there are five atypical varieties which are emphasized by Igersheimer (5) 1) annular keratitis (Vossius) 2) radial opacities of the folds of Descemet's membrane 3) nodular parenchymatous keratitis 4) phlyctenular affections in typical interstitial keratitis and 5) gumma of the cornea

Annular keratitis This form of keratitis was first described by Vossius It usually occurs in children under ten years of age but may also develop in older persons in acquired lues A group of deep infiltrates are arranged

in annular fashion in the center of the cornea associated with concentric folds in Descemet's membrane Gilbert has pointed out that this ringlike opacity is a passing stage in diffuse interstitial keratitis

Radial folds in Descemet's membrane This condition occurs rarely and Igersheimer has witnessed it only twice It is not really a separate form of parenchymatous keratitis rather it occurs in the course of the latter disease It is characterized by radial linear opacification of the cornea accompanied by folds in Descemet's membrane

Nodular parenchymatous keratitis This occurs very rarely Dense nodules of the cornea become thicker the longer the disease continues

Phlyctenular keratitis Since allergy plays an important role in parenchymatous keratitis it is not surprising that in a certain number of cases the disease assumes a phlyctenular appearance There are two subgroups of this type The first is a protruding yellow solitary nodule on the anterior

Gumma of the cornea In the gummatous type of interstitial keratitis a large dense yellowish white opaque area develops in the center of the cornea and threatens to slough but rarely does However when this occurs a large superficial area of the cornea may break down leaving a ragged ulcerated surface

Treatment

The special character of interstitial keratitis as compared with other manifestations of both congenital and acquired syphilis was and still is emphasized by lack of response of the disease to specific antibiotic therapy In fact not infrequently such treatment appears to aggravate the condition rather than help it Moreover cases have been observed where single doses of arsenicals in acquired lues have initiated the sudden onset of interstitial keratitis in hitherto normal eyes (2) Such reactions might be considered Jarisch Herxheimer episodes further evidence for the allergic character of interstitial keratitis Penicillin may also result in similar Herxheimer type reactions (6)

Prior to the advent of the steroids major reliance was placed on fever therapy of all types of which the most commonly used was foreign protein—especially intravenous typhoid injections The hypertherm was utilized in severe cases when available The most outstanding result of such treatment was the almost immediate improvement in the associated iridocyclitis which is indeed a major problem in the management of the disease Atropine in itself often was inadequate without this essential adjuvant Once the uveitis was under control foreign protein was needed less often

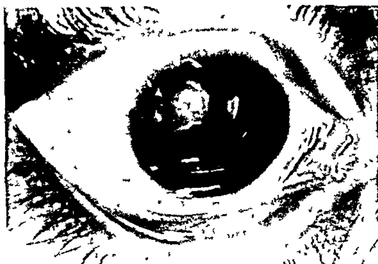


Fig 99 Luetic interstitial keratitis benefited by topical steroid therapy

At the present time the use of corticosteroids both systemically and topically appears indicated along with mydriatics as the first approach to treatment Conflicting reports as to the efficacy of the steroids appear to be accounted for largely by differences in dosage and method of administration Drews Barton and Mikelsen (7) reported beneficial results in 17 patients treated topically with cortisone Since relapse occurred after the medication was discontinued in the first three cases these authors continued a daily dose of cortisone ointment for long periods in the other cases One patient discontinued the drug after eight months of therapy and relapsed ten days later while the others maintained their improvement Thus it is apparent that corticosteroid therapy must be continued for long periods of time Klauder and Meyer (8) noted dramatic *clearing of the cornea in mild and moderate cases Cortisone prevented* the formation of superficial vascularization which constitutes the salmon patch These authors did not continue with the use of cortisone because they felt that it prevents local immunity and cure Instead they tried testosterone and thyroid extract and fever therapy From their results they felt that the most valuable treatment is fever antisyphilitic and thyroid therapy In view of the use of corticosteroids for long periods of time in other conditions such as sympathetic ophthalmia we see no valid reason why these drugs cannot be used for periods of over a year if necessary for so serious a disease as interstitial keratitis It is our impression that they were not given an adequate trial except by Drews

Barton and Mikelsen Our own small experience with steroids has been good

The use of foreign protein and other forms of fever therapy at times may be required The use of penicillin in a covering action to control other manifestations of active lues appears indicated but in view of the allergic basis for the keratitis must be used with caution

EXPERIMENTAL STUDIES OF THE CORNEA RELATED TO INTERSTITIAL KERATITIS

In 1855 Hutchinson began a series of observations on interstitial keratitis These outstanding studies examples of what keen clinical methods can accomplish were enlarged and elaborated upon in a Clinical Memoir of Certain Diseases of the Eye and Ear Consequent in Inherited Syphilis published in 1863, which established with certainty, that interstitial keratitis was due to congenital lues Wessely (9) was the first (1911) to prove that a pathologic picture identical with interstitial keratitis could be produced by an allergic mechanism indicating 'anaphylaxis' as the cause of the luetic variety

The cornea is an ideal organ for the study of allergic phenomena because it is both transparent and dependent for its nourishment on the vessels of the conjunctiva and sclera Thus all of the cellular components of the inflammatory reaction have to be brought in from the limbus by the blood vessels Moreover the degree of reaction can be gauged by the amount of opacity which develops in the cornea It was the appreciation of these facts which led Wessely von Szily and Arisawa (10) Schieck (11) Igersheimer (5) Lowenstein (12) and others to study allergic reactions of the cornea in an attempt to elucidate the pathogenesis of parenchymatous keratitis and the nature of the allergic response in the cornea itself

Wessely (9) first injected small amounts of either ox serum or horse serum into the parenchyma of rabbit corneas At the site of the injection there immediately occurred the usual mechanical opacity of the parenchyma which disappeared with complete resorption after a short time In ten to fourteen days in the absence of further exposure to antigen twenty to thirty per cent of these eyes developed deep parenchymatous

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touched fellow eye in every instance (one hundred per cent) anaphylactic inflammation occurred This resembled greatly the typical picture of congenital luetic interstitial keratitis It would appear to us that in those cases where a keratitis occurred spontaneously after one injection only once the eye had become sensitized enough of the original serum had remained in situ to excite an allergic interstitial process

This important and fundamental contribution was confirmed by other investigators. Von Szily and Arisawa (10) who were prominent among these furthermore showed that after original sensitization of the cornea by direct injection was effected intravenous injection of the same foreign serum 14 days later was capable of producing severe interstitial keratitis in this eye but not in the fellow eye.

That similar allergic reactions of the cornea could be produced by injections of egg albumen was shown by Julianelle and Bishop (13) and others. Schoenberg (14) obtained similar results with injections of human albumin. However, with tuberculin he could not produce an interstitial reaction.

THE ROLE OF ALLERGY IN INTERSTITIAL KERATITIS

There are two theories of the role of hypersensitivity in the development of interstitial keratitis: 1) the theory of the correlation between the immunity of the cornea and that of the remainder of the body, and 2) the theory of autosensitization caused by antigenic action of organ specific corneal protein.

Correlation between immunity of the cornea and the remainder of the body. This theory was strongly supported by Igersheimer (5). He believed that deposits of spirochetes remain in the corneal tissue from the fetal period. When these spirochetes are destroyed their breakdown products are freed and remain in the cornea—which is relatively isolated from the general metabolic process; thus the cornea becomes hypersensitive. When at a later date specific antigenic material gets into the blood stream a small amount may reach the cornea and cause a local anaphylactic inflammation, i.e., parenchymatous keratitis.

*Schieck (15) has elaborated this idea. According to him the dying spiro*chetes remain in the cornea acting only as foreign antigens—whereas in the other portions of body an active immunity eventually develops. Thus for a while there exists the condition that the organism creates specific antibodies against the spirochetal albumin but this state of affairs cannot be attained by the cornea because the immune bodies cannot reach it. It requires only a minor impetus to disturb the status quo and to bring the two components of the local allergic reaction (antigen and antibody) into contact with each other by the infiltration of the antibodies into the corneal tissue. It seems to us that according to this idea the important distinction between allergy and immunity must be emphasized. In the cornea only allergy has occurred, elsewhere immunity has been achieved. In this manner one might explain not only spontaneously occurring interstitial keratitis but also those cases which are set off by trauma or any other exciting process in patients with congenital lues. The bilateral occurrence of this condition can be explained in a similar manner.

In 1929 in a critical analysis of these theories Riehm (16) emphasized that only this type of explanation ties in with the results of the experiments of Wessely

Autosensitization caused by antigenic action of organspecific corneal albumin Using luetic rabbits Lowenstein (12) demonstrated that intracorneal injection of human serum caused the development of dense corneal infiltration in a large majority of cases Healthy animals on the other hand could easily tolerate the intracorneal injection of such serum A similar parenchymatous inflammation occurred when Lowenstein disturbed the corneal nutrition in luetic animals by trauma to the limbus and the sclera Histologic studies in some rabbits with lues of long duration which had developed spontaneous interstitial keratitis showed massive scleral round cell infiltrates which compressed the ciliary vessels Lowenstein concluded that in such rabbits there exists an increased sensitivity of the tissues to foreign protein

The corneal tissue appears to have a tendency to local allergic inflammatory reactions Both Igersheimer and Schieck refer to an allergic reaction in interstitial keratitis where the spirochete acts as the antigen Conversely however Lowenstein has maintained that an autogenous antigenic resorption of denatured corneal tissue occurs He feels that the pericorneal vascular involvement disturbs the nutrition of the cornea resulting in such degeneration This produces an autogenous antigen

It would appear from Lowenstein's thoughts that direct specific spirochetal invasion does not of itself excite the allergic interstitial reaction While the luetic process may alter the vascular structures about the cornea the acutal antigen is the altered tissue albumin of the cornea which has been changed by the disease

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18

ALLERGY OF THE SCLERA

Unless one accepts an allergic mechanism as important in the pathogenesis of affections of the sclera, it is difficult to explain most instances of scleritis and episcleritis. In fact, while scleritis in itself is a relatively infrequent disease, the percentage of scleral inflammations of probable allergic origin is very high—perhaps higher than in any other ocular structure. The sclera appears to be rather resistant to all types of infections, burns, chemical trauma and neoplastic proliferation as compared with the more delicate external tissues of the eye, such as the conjunctiva and cornea. Furthermore, the widespread use of anti-infective agents, in addition to the control of syphilis and tuberculosis, has resulted in the lessening importance of infection in the causation of scleritis. Even the rare metastatic or traumatic pyogenic infections encountered previously have now been in great measure eliminated. Thus at the present time possibly the most important type of scleritis where actual organismal invasion occurs would appear to be leprotic; this arises along with other leprotic manifestations and is generally in itself not a diagnostic problem.

The sclera appears to be ignored in the experimental investigation of allergic phenomena by both immunologists and ophthalmologists. This is not surprising for three reasons: 1) the eye offers several other tissues better suited for general allergic studies, 2) the sclera is not directly exposed, and 3) it is not a tissue concerned in the actual visual process. We are thus forced to depend chiefly on clinical observations for the evaluation of the different allergic mechanisms that appear to operate in the production of scleritis. The field is further narrowed in that the nature of the scleral tissue as such appears to preclude contact allergy. On the other hand, its collagenous structure and good blood supply might explain

TABLE 10

Allergy of the sclera

1 *Atopic allergy (immediate reaction)*
  a Inhalants episcleritis
  b Food allergy episcleritis
2 *Microbial allergy (delayed reaction)*
  a Streptococcus Staphylococcus episcleritis scleritis
  b Tubercle bacillus scleritis sclerosing keratitis
  c Other microorganisms episcleritis scleritis
3 *Collagen diseases (mechanism?)*
  a Gout rheumatic fever rheumatoid arthritis periarteritis nodosa scleritis episcleritis

both the atopic and the microbial allergies that occur so commonly as well as its involvement in the ill defined and probably allergic reactions of collagen diseases

CLASSIFICATION

On the basis of known allergic mechanisms and clinical manifestations allergic reactions of the sclera may be classified as in table 10

CLINICAL PICTURE OF EPISCLERITIS AND SCLERITIS

Although textbooks customarily describe various apparently clearly differentiated forms of scleral inflammation these so called entities are not so readily distinguishable in practice and would appear to be gradations of essentially the same pathologic process In the superficial variety episcleritis only the episcleral tissue and the superficial layers of the sclera are involved In the deeper variety scleritis the entire thickness of the sclera is affected Thus it is difficult to draw a line between the two conditions Whether episcleritis fugax which comes on in sudden short attacks and may recur for years is a special entity is also open to question Annular scleritis would appear to be an extension of a localized process The rare brawny scleritis seems to be a particularly severe form of the disease Scleromalacia is a degenerative process occurring in elderly individuals

The sclera appears to give a uniform reaction regardless of the etiologic agent Thus the type of response that most commonly occurs cellular (usually lymphocytic) infiltration and vascular engorgement along with swelling and edema of the scleral lamellae is essentially nonspecific Sclerosing keratitis in which the adjacent cornea becomes involved may be an exception it seems to occur most commonly as an allergy to tuberculoprotein It is interesting to observe in this connection that phlyctenulosis has a similar predilection for the limbal region and is also chiefly caused by allergy to the same product

Diagnosis All forms of scleral inflammation occur much more commonly in women Furthermore attacks are often noted at the menstrual period Persons with known allergic backgrounds appear to be particularly susceptible to scleral inflammations The symptoms may range from minimal discomfort and lacrimation in the most superficial varieties to severe pain and marked photophobia in true scleritis The milder types are of short duration perhaps one to two weeks but tend to recur When involvement is deeper the condition is more severe and more per i tent

The objective signs of scleral inflammation are quite diagno tic These are the characteristic purplish red color the tenderness on pres ure and the persistence of injection after the instillation of vasoconstrictors In the mildest form of inflammation a diffuse congestion and edema of the episcleral tissue and the conjunctiva over it may occur In other cases episcleritis is typically characterized by a flat bulbar inflammation u ually quadrantic in area of dark red or purpli h color In the so called nodular variety a slightly raised hard immovable nodule occurs When the entire thickness of the sclera is involved the purplish color is more marked and tenderness may be extreme In severe cases uveitis and secondary glaucoma may complicate the picture

ATOPIC REACTIONS

The evanescent nature of scleritis and episcleritis often makes it difficult to prove conclusively the exact causation of the inflammation Thus in allergic reactions of the immediate variety affecting the sclera it i sometimes impossible to pin point the responsible allergen even though the process is clearly of the atopic type Most such allergies appear to arise from foods occasionally inhalants are responsible

Food Allergies

On occasion one is fortunate enough to observe a sufficiently clear cut example of food allergy causing episcleritis or scleritis to justify the conclusion that such allergy plays a definite role in the causation of scleral disease In our experience seafood appears to be an important allergen (fig 100) A patient who was sensitive to fi h in general would develop transitory episcleritis on many occasions following the ingestion of such food In this instance mo t attacks were so mild that the patient did not refrain from eating fish As a result we were able on three distinct occasions to correlate the sudden occurrence of episcleritis with exposure to fish Shellfish seem to be responsible for similar reactions in other patients However the statistical importance of seafood may be more apparent than real since patients more readily remember eating it than other more commonly consumed foods which can also cau e allergic reactions



FIG 100 Nodular episcleritis apparently related to allergy to various seafoods

In general the identification of the food causing any allergic process is difficult, the sclera is no exception This might explain the paucity of proven instances of scleritis due to food allergy Food allergies appear to be relatively complex entities requiring a special set of circumstances for their clinical evolution On one occasion allergic reaction may follow the ingestion of a specific food while at other times the same individual may eat the same food without developing any allergic reaction at all The allergic reaction may result only when the food is altered during the digestive process—a situation that may not always occur Often an individual allergic to a raw food may eat it when cooked without reacting the reverse may sometimes occur While these factors militate against the recognition of the offending allergen in such an isolated structure as the eye occasionally even if the eye itself is not involved in every episode clues may be obtained from reactions occurring elsewhere in the body such as urticaria

Inhalant Allergies

We have encountered recurrent episcleritis in a patient (fig 101) with severe ragweed hay fever which occurred only during the season of pollination After successful desensitization no further episodes were noted At times it appears that enough antigen is absorbed in hay fever to cause mild general systemic reactions On rare occasions the eye may be affected with resultant iridocyclitis and apparently scleritis However it should



Fig 101 Episcleritis associated with allergy to ragweed. This cleared after specific desensitization

be borne in mind that other allergies, especially to foods, clinically dormant at other times may erupt during the increased general hypersensitivity which may occur when the allergic patient is suffering from severe hay fever symptoms.

Although we have no experience with other inhalants and we know of no reports on the subject in the literature, it is possible that on rare occasions other pollens and dusts may play a role in the causation of scleral disease.

MICROBIALLERGIC REACTIONS

Many instances of scleritis appear to be best explained on the basis of microbial allergy. In fact, if we consider certain of the collagen diseases, such as rheumatoid arthritis, to be due to bacterial (streptococcal) allergy, then it would be safe to say that most scleritis has a microbiallergic origin. Clinical and confirmative laboratory experiences indicate that such allergy is in general evoked chiefly by three organisms: Streptococcus, Staphylococcus and the tubercle bacillus. While it is probable that many other organisms incite allergic scleral reactions, the evidence for this is less clear cut. However, the well known relationship between scleritis and what was originally considered focus of infection—but which we prefer to call an antigenic focus (see chap 19)—indicates that while these organisms dominate the picture, many others, such as enteric bacilli



FIG 102 Resistant recurrent episcleritis associated with chronic sinusitis

and perhaps even parasites may be incriminated The present day importance of syphilis in the etiology of scleritis is difficult to evaluate In our experience it would appear negligible Rarely diffuse circumcorneal scleritis may occur in interstitial keratitis but this reaction is not a typical type of recurrent scleritis

Streptococcus

The antigenic properties of the Streptococcus have been mentioned in chapter 4 and are detailed in chapter 19 There appears to be no question that allergy to streptococcal products plays an important role in a number of general diseases and as far as the eye is concerned in scleritis and uveitis The association of scleritis and uveitis with rheumatoid arthritis is well known On rare occasions simultaneous involvement of both structures may be encountered However in rheumatic fever another disease in which streptococcal allergy appears etiologically important nongranulomatous uveitis does not seem to occur and scleritis is rather infrequent We do not know the explanation for this apparent discrepancy in the behavior of the eye in these two generalized diseases the age incidence may be a factor

Staphylococcus

The importance of the Staphylococcus in the causation of allergic reactions of the outer eye has been stressed in chapters 4 and 13 Since microbial allergic conjunctivitis dermatitis and keratitis (chap 13) are such

common clinical entities one might assume that scleral reactions arising on a similar basis should occur more frequently However on the basis of our experience such scleritis is relatively rare In fact staphylococcal allergy almost always appears to require a direct local infectious focus for its occurrence while streptococcal allergy usually arises from a distant antigenic focus via the blood stream This observation is in line with what is known about nongranulomatous uveitis We have encountered relatively localized superficial nodular scleritis in persons with long standing blepharoconjunctivitis due to pathogenic toxin producing staphylococci The patients so affected exhibited marked hypersensitivity to staphylococcal products on skin testing On occasion however focal staphylococcal infection appears to cause scleritis

Tubercle Bacillus

Over the years tuberculosis has shared equal importance with rheumatism in the etiology of scleral disease With the acceptance of bacterial allergy as an important disease mechanism it is now believed that most instances arising in the course of tuberculosis are not in themselves infectious but instead are due to allergy to tuberculoprotein It appears that when the adjacent cornea becomes involved in the course of scleritis (sclerosing keratitis) (fig 103) the etiology of the process almost always arises on this basis The pathogenesis of scleritis due to hypersensitivity

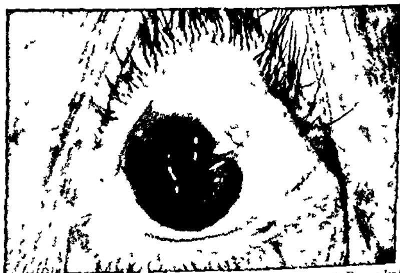


FIG 103 Sclerosing keratitis Strongly positive tuberculin skin test Deep scleritis responded to x ray therapy

to products of the tubercle bacillus resembles that of phlyctenular kerato conjunctivitis which often has a similar etiology To a large extent the inflammatory response of the sclera to tuberculoprotein is similar to that of the conjunctiva the limbal region seems to be the area of predilection with corneal extension not uncommon Like other entities associated with tuberculosis, scleritis arising on this basis is waning

SCLERITIS IN COLLAGEN DISEASES

The collagenous structure of the sclera may explain the frequency of the occurrence of scleritis as a manifestation of certain generalized collagen diseases The most important of these is rheumatoid arthritis (fig 104) in which recurrent scleritis is so commonly encountered Because of the role that streptococcal allergy may play in this disease scleritis arising on this basis has been discussed in the previous section The rare scleritis occurring in rheumatic fever has also been mentioned

Our increasing awareness of the frequency of gout (fig 105) especially in the milder and subclinical forms, has highlighted the importance of realizing that recurrent episcleritis may provide the first clinical clue to the diagnosis In fact it is our opinion that blood uric acid determinations should be performed on all patients with scleritis and nongranulomatous uveitis Although gout is believed to be a metabolic disorder certain facets of its clinical behavior suggest that the disease has allergic overtones For example gouty attacks may be precipitated in atopic individuals by ex



Fig 104 Recurrent episcleritis in rheumatoid arthritis



Fig 105 Episcleritis in gout

posure to or ingestion or injection of the offending antigen similarly exposure to cold may evoke an exacerbation This may explain the association of an apparently allergic form of scleritis with gout

Scleritis likewise occurs in periarteritis nodosa (fig 106 and 107) another collagen disease in which allergy appears to play an important etiologic role Scleral involvement is not uncommon in this relatively rare disease

TREATMENT

In the past the treatment of scleritis of nonspecific origin was essentially symptomatic It consisted basically of hot compresses mydriatics salicylates and fever therapy In severe persistent instances radiotherapy was and still is a valuable therapeutic modality The elimination of foci of infection continues to be a procedure of some value In some instances infected teeth appear to be the cause of recurrent attacks

The present day use of corticosteroids usually locally but sometimes systemically offers the best single therapeutic approach In those cases which respond (the majority) improvement may be dramatic Certain cases however appear resistant to hormonal therapy In fact at times steroids seem to aggravate the inflammation In such instances other types of treatment noted above are necessary

It is possible that steroid resistant scleritis is of nonallergic origin and that the disease has an allergic basis in patients who respond





Fig 106 (*above*) Scleral nodule with corneal involvement in periarteritis nodosa Rapid and dramatic resolution with steroid therapy (courtesy of Dr W B Howard)
Fig 107 (*below*) Cutaneous nodules in periarteritis nodosa (same patient as fig 106) (courtesy of Dr W B Howard)

When scleral inflammation is associated with a specific entity such as gout special measures (diet colchicine or Butazolidine) are indicated Where specific allergens such as food or inhalants are responsible avoidance of such products—or desensitization when feasible—should be carried out If infection plays a role in the production of antigens that incite a scleral allergic reaction specific anti infective measures are indicated such as the newer antitubercular drugs chemotherapeutics in leprosy and at times vaccine or toxoid therapy

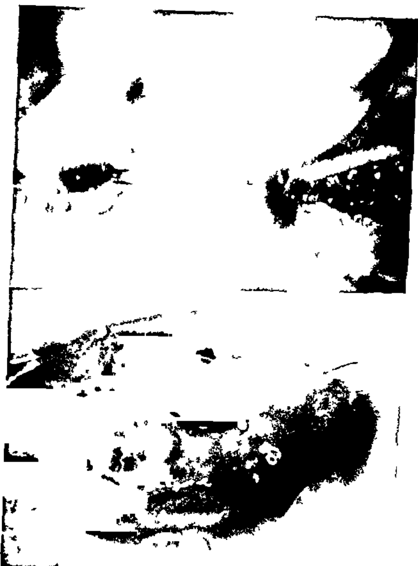


Fig 108 Serous tenonitis Note chemosis and inability to abduct affected eye
Fig 109 Serous tenonitis (close up)

TENONITIS

Except for the rare instance of tenonitis arising from direct infection such as that complicating trauma or extraocular muscle surgery, the obscure etiology of tenonitis appears best explained in certain instances on the basis of allergy

Tenonitis is most commonly encountered as the primary serous variety occasionally the condition may arise as an extension of scleritis The condition is usually characterized by a sudden onset of marked chemosis especially of the bulbar conjunctiva impairment of ocular motility in one or more fields of gaze, and slight proptosis (figs 108 and 109) There is associated edema of the lid Both local pain and pain on ocular movement may be present In tenonitis chemosis is marked and proptosis slight in orbital cellulitis the reverse occurs The course of this rare disease is essentially benign, although at first it may assume an alarming appearance After a varying period of time perhaps four to six weeks without treatment the condition clears spontaneously In general it affects older people, especially those suffering from gout or rheumatic affections

The rarity of the disease makes etiologic evaluation difficult Its exudative character, its transient, recurrent yet benign course its association with collagen diseases its relationship and similarity to scleritis and its response to corticosteroids and foreign protein therapy all suggest that an allergic component may play a role in its causation However we know of no known instance where tenonitis has arisen on the basis of atopy such as food allergy That microbial allergy may operate is suggested by its association with rheumatoid arthritis and infective antigenic foci In this regard it is possible that the chemosis and other ocular findings in trichiniasis are due to tenonitis arising secondary to muscle infestation either as toxic or allergic response to products of the trichinella

Corticosteroids both local and systemic provide the most satisfactory form of therapy for tenonitis It is interesting to note that these hormones are equally effective in ocular trichiniasis In severe cases mydriatics and other supportive measures are indicated Chief among these are salicylates

19

ALLERGY OF THE UVEA

Robert S. Coles, M.D.

It is generally accepted that allergy plays an important and often essential role in the pathogenesis of most types of endogenous uveitis. In view of the importance of uveal disease in terms of the prolonged period of disability and the serious visual damage that may result, allergy of the uveal tract should be considered the most important form of ocular allergy encountered even though its incidence is less than some other type of ocular sensitivity. At the present time an allergic mechanism is believed primarily responsible not only for the obviously allergic reactions of the uvea occurring during serum sickness, angioneurotic edema and other immediate forms of allergy, but also for the inflammatory process characteristic of the rather common nongranulomatous sterile form of endogenous uveal inflammation. This delayed allergic reaction is believed to be of the microbial type. Another form of allergic response to autogenous allergens also appears to operate in the causation of sympathetic ophthalmia and in endophthalmitis phacoanaphylactica. Even in those granulomatous types of uveitis where microorganisms may be demonstrated, such as tuberculosis, a secondary microbial allergy often alters and aggravates the inflammatory state. While further investigations may reveal limitations of this point of view, for the time being an allergic pathogenesis would seem to offer the most likely solution to the difficult etiologic and therapeutic problems relative to uveal inflammation.

CHANGING ETIOLOGIC CONCEPTS IN UVEITIS

The evolution of the concept that many otherwise unexplained forms of uveitis might be considered as allergic in pathogenesis was slow, even though the excellence of uveal tissue as an experimental anaphylactic

shock organ was recognized and this knowledge utilized only a few years after the concept of allergy was first proposed. Two lines of investigation necessarily preceded acceptance of this concept. The first was the unquestioned acceptance of the protean manifestations of allergic diseases and this required a period of almost fifty years. The second was the precise delineation and classification of the different forms of uveal disease permitting those entities with the clinical characteristics suggestive of hypersensitivity to be studied separately with this new pathogenetic approach in mind.

Bacterial Infection

Although many observers had noted the association of uveitis with general infections such as syphilis, tuberculosis and gonorrhea as well as in the course of rheumatic diseases, the great impetus to the concept that endogenous uveitis was infectious in nature coincided with advances in the field of bacteriology. By the end of the nineteenth century it was definitely established on both experimental and clinical evidence that in certain of the more chronic forms of endogenous uveal inflammations accompanying tuberculosis, syphilis and leprosy, actual bacterial invasion could be demonstrated. Similarly, it was shown that certain pyogenic organisms such as the Streptococcus, Staphylococcus and pneumococcus could produce acute purulent infections, particularly in the course of septicemia. The authority of many of the investigators who stressed the probable role of syphilis, tuberculosis and rheumatic diseases, but could not prove their thesis, was responsible in leading others to consider the paramount importance of these diseases. When, after the advent of serologic tests, it was possible to exclude syphilis from the differential diagnosis, the presumed incidence of tuberculous etiology became even greater. The frequency of clinical tuberculosis as well as the extremely high incidence of positive tuberculin tests tended to lend support to the view of an etiologic association between tuberculosis and chronic uveitis. However, it was only recently made clear that the importance of tuberculosis as a cause of uveitis either has been greatly overestimated in the past or has waned with the decline in this disease.

Focal Infection

There nevertheless were a considerable number of instances of uveitis in which there was no evidence of local bacterial invasion. To account for this, the still bacterially oriented observers utilized the concept of focal infection or what we in this book prefer to call an antigenic focus. Because on this basis some of the major tenets of this theory still appear applicable, it will be discussed in some detail.

The theory of focal infection as a cause of uveitis began with Nettleship (1) who, in 1879, described a patient with exudative choroiditis presumably due to a dental infection. In 1911 Butler published a paper (2) in which he attributed the uveitis in twelve of one hundred patients to oral, nasal and other types of infection. Two years later Lang revised this figure to forty per cent (3). In the United States Billings (4) accepted the theory of focal infection and became its ardent proponent.

The concept of focal infection assumes that a remote and circumscribed area, usually communicating with a mucous or a cutaneous surface, is responsible for the dissemination of bacteria to other parts of the body via the lymphatics or the blood stream. Thus, tissues dissimilar and distant from the original focus may react to local invasion with local inflammation. Commonest sites for the primary infection are said to be the teeth, tonsils and sinuses, but any tissue in the body may be involved—as, for example, the gallbladder, appendix, small or large bowel and prostate. The mode of transmission from the primary to the secondary focus of infection has been attributed to 1) direct bacterial metastasis from the primary site of infection, 2) the toxins liberated by the bacteria, 3) bacteria of attenuated virulence when they reach the secondary site.

Experimental evidence for this theory rested, at best, upon tenuous grounds. Rosenow (5) claimed to have cultured the same streptococcus from the circulating blood, the tonsils, the affected joint capsules and the alveolar processes of the teeth. He explained the selective affinity exhibited by certain organisms for certain tissues by invoking a specific tropism or affinity.

Other investigators were unable to duplicate or confirm the previously reported findings in man or in experimental animals. However, once postulated, the theory of focal infection was accepted by ophthalmologists as a diagnostic and therapeutic tool in managing patients with refractory conditions. Even now, when most branches of medicine have discarded this concept, some ophthalmologists continue to adhere to this theory in the causation of uveitis despite reports published by Guyton and Woods in 1941 (6), by Woods and Guyton in 1944 (7), and by Hughes in 1943 (5), indicating little correlation between eye diseases and foci of infection.

Allergy

As the controversy over focal infection went into slow decline, accepted by some and denied by others, more and more ophthalmologists began to lean towards an allergic etiology. In 1947 Woods, one of the early and leading proponents of this concept, made an important contribution to the study of uveitis when he classified uveal inflammation into two main groups (8): 1) a granulomatous variety which involved actual organismal

invasion and proliferation in the uveal tract and 2) a nongranulomatous form which he believed to be allergic in origin and to be precipitated by antigens liberated from some distant focus in the body The granulomatous variety, he felt could be modified also by the allergic reaction of the invaded tissues to the organism This concept of allergy as a responsible mechanism for uveal inflammation was not a new one There had been many previous scattered reports, commencing with Elschnig's (9 10) studies on sympathetic ophthalmia in 1910 this was followed by many experimental studies demonstrating the importance of allergic phenomena in the eye However, it remained for Woods (8 11) to collate previous experimental work and demonstrate the importance of allergy in the pathogenesis of uveitis This concept explained many of the inconsistencies in the theory of focal infection and made the latter more readily acceptable to some Although the concept of an allergic mechanism is now widely accepted as an explanation of many forms of uveitis this theory does not supply the full answer and it must be considered tentative for the present

Viral Infection

The as yet relatively unexplored field of virology may offer the necessary information to complete the gaps in our knowledge of the pathogenesis of uveitis It has been definitely established (13) that nongranulomatous uveitis may complicate such viral diseases as mumps influenza herpes simplex herpes zoster, smallpox and chicken pox Certain aspects of the clinical course of such uveitis indicate that the reaction may be, at least in part a manifestation of viral allergy The causation of the uveitis occurring in Reiter's disease and in Behcet's syndrome may be viral in origin as well In support of this Sezer (14) states that he has isolated a virus from the chorioretinal fluid and the blood in the latter disease

Uveitis Associated with Disease of Probable Allergic Etiology

Iritis has been observed in the course of periarteritis nodosa The choroid is more frequently involved in this disease Such manifestations are discussed in chapter 21

THE CLASSIFICATION OF ENDOGENOUS UVEITIS

In the United States in England and to a lesser degree in other countries the current concepts for classifying endogenous uveitis stem from a paper published by Woods in 1947 (8) and since amplified in other publications (11) According to Woods all types of endogenous uveitis consist of a nonpurulent inflammation involving or originating in the uveal tract, secondary to a systemic infection elsewhere in the body From this classification were excluded all primary uveal degenerations vascular dis

turbances metabolic disorders and inflammations from contiguous structures Endogenous uveitis was then divided into two major types known as the nongranulomatous and the granulomatous forms The terms granulomatous and nongranulomatous stem from the different histologic characteristics found on pathologic study of enucleated eyes According to Woods these two types of uveal inflammation are entirely dissimilar in clinical appearance pathogenesis and microscopic alterations However it must be observed that both clinically and pathogenetically these distinctions are not always clear cut and indeed the pathologic picture in both processes may overlap so as to render certain differentiation between them impossible Therefore sometimes it is much simpler clinically to classify uveitis into anterior or posterior varieties

Ashton (12) and others have indicated that the terms granulomatous and nongranulomatous are without any real meaning from the histopathologic point of view In the past pathologists utilized these terms to describe the proliferative and chronic reactions which characterize syphilis tuberculosis and leprosy This usage has become obsolete since these reactions are now regarded as examples of chronic inflammation manifesting histologic features that are to be found in almost any chronic inflammation Ashton points out that practically any inert irritant such as talc beryllium wood and silica is capable of inducing similar proliferative granulomatous responses

Granulomatous Uveitis

The granulomatous reactions tend to involve the entire uveal tract although the choroid is the site of predilection In this form of the disease with certain exceptions actual invasion of the uveal structures by living organisms from some distant focus is frequently demonstrable In response to the presence of the organism the invaded tissue reacts with a proliferative reaction of variable degree depending upon the virulence of the invading organism the hypersensitivity of the involved tissue and the immunity of the patient

Clinically this form is characterized by an insidious onset with a chronic low grade aqueous flare and cells in the anterior chamber the presence of mutton fat keratic precipitates on the endothelium the formation of heavy posterior synechiae and eventually of anterior synechiae and the appearance of nodules on the iris If the disease is unchecked eventual destruction of the eye occurs In the posterior uvea actual exudation into the retina occurs characterized by circumscribed areas of edema Outpouring of inflammatory cells and debris into the vitreous may be so dense that details of the fundus may be obscured

The essential pathologic features consist of the invasion of the uveal

structures by living nonpyogenic organisms which induce a granulomatous inflammation characterized by the mobilization and proliferation of large mononuclear wandering cells which eventually become epithelioid. Giant cells forming from the fusion of these epithelioid cells aggregate into large nodules resembling tubercles. Considerable necrosis occurs in adjacent structures. Reparative processes result in fibrosis and gliosis of the involved area. Usually an associated outpouring of lymphocytes and plasma cells at the site of infection is noted although this may also occur in areas remote from the granuloma.

The destruction which results from tissue invasion by organisms is determined in many instances such as tuberculosis by the delicate balance between immunity and hypersensitivity in the host. Thus equivalent inoculums in two different eyes can give rise to varying degrees of inflammation and tissue destruction depending upon the underlying hypersensitivity of the tissue and its natural or acquired immunity. These reactions will be discussed in detail when the individual types of posterior uveitis are considered. According to Woods (11) endogenous granulomatous uveitis can be divided into the following types 1) nonpyogenic organisms pathogenic for man tuberculosis syphilis brucellosis leptospirosis leprosy 2) filterable viruses and rickettsia herpes simplex herpes zoster Behcet s disease Vogt Koyanagi Harada s disease lymphogranuloma venereum 3) protozoan infections toxoplasmosis trypanosomiasis 4) fungus infections actinomycosis blastomycosis histoplasmosis 5) helminthiasis nematodes cestodes 6) unknown agents sarcoid sympathetic ophthalmia. Those granulomatous diseases in which the allergic component plays an important role in the pathogenesis will be discussed in greater detail in a later section of this chapter.

Nongranulomatous Uveitis

The nongranulomatous forms of uveitis are predominantly localized in the anterior segment of the uveal tract and are considered to be reactions due to tissue hypersensitivity.

Clinically nongranulomatous uveitis affecting the iris and ciliary body consists in the acute onset of an inflammatory reaction in the anterior chamber. This is characterized by an intense aqueous flare with many fine cells visible in the beam of the slit lamp. Marked circumcorneal injection is present. The corneal endothelium is dotted with very fine precipitates which are often so tiny that they are missed. A sero fibrinous exudate occurs along with iris stromal edema which obliterates the normal delicate tracery and may produce miosis. Pain may be very severe.

When the disease affects the posterior uvea the pathogenesis is the same but because of the different nature of the involved tissues the re

action varies somewhat A fine vitreous haze is present resulting from a cellular exudation from the ciliary body *and retina There often occurs* a generalized subretinal edema most marked in the region of the disk Frequently this area is circumscribed and focal and simulates the pic*ture of a granulomatous reaction In such instances* there is less pain

Characteristic of the attacks of nongranulomatous uveitis is the fairly rapid resolution and complete healing of the involved structures without sequelae However permanent structural changes similar to those elicited in the Arthus phenomenon may occur as a result of repeated attacks These consist of thrombosis in the nutritive vessels of the uvea leading to hemorrhage, necrosis and sloughing The end stages of repeated cumulative attacks of nongranulomatous uveitis appear as patches of iris atrophy posterior and anterior *synechiae, seclusio pupillae, cyclitic membranes* and phthisis bulbi

In this primarily allergic type of reaction, the pathologic picture *consists of capillary dilatation with an outpouring of cells—at first* polymorphonuclear leukocytes These are then rapidly replaced by mononuclear cells—lymphocytes plasma cells and large macrophages Examination of the affected structure when healed reveals only pin point areas of necrosis or atrophy Subsequent attacks lead to atrophy gliosis and fibrosis resulting in adhesions and scarring with eventual disorganization and destruction of the eye

Woods postulated that the nongranulomatous forms of uveitis involving primarily the iris and ciliary body are hypersensitivity reactions He further felt that the usual cause of the hypersensitivity is bacterial in nature and is of the delayed tuberculin variety of reaction as was de*scribed in chapter 1 He assumed that the eye is initially* sensitized to specific organisms as a result of a transient bacteremia originating from either a distant focus of infection a generalized infectious process or from *mucous membrane absorption That transient bacteremias* commonly occur is well established—as for example immediately following a tooth extraction For the eye to become sensitized it is necessary that there be actual contact between the organism *living or dead and the ocular tissues* Later, as a response to new infection with the same organism or to its soluble products a hypersensitive (allergic) reaction occurs in the previously sensitized ocular tissue Although it is possible to incite an ana*phylactoid reaction* a delayed bacterial response usually occurs The most commonly implicated bacteria are the streptococci In the past when gonorrhea was more common the gonococcus a definitely antigenic organism was often considered responsible The Staphylococcus is only rarely found to be a sensitizing agent because its antigenicity for uveal tissue appears to be low Furthermore staphylococci are not *frequently*

found as the offending pathogens in foci of infection Pneumococci do not seem to play a significant role in anterior uveitis

THE BASIS FOR ALLERGY AS A CAUSE OF UVEITIS

The belief that allergy is responsible for most attacks of nongranulomatous uveitis and that allergy can also markedly influence the course of the granulomatous forms of uveitis is more than speculation The bases for this belief are anatomic, experimental and clinical

Anatomic Evidence

A study of allergic states reveals that those organs generously endowed with an abundant vascular supply are among the most prominent shock organs' in the body Such common sites for allergic reactions include the bronchial tree, the nasal mucous membranes and the conjunctiva

The anatomy of the uveal tract the vascular layer of the eye is such that it offers a fertile terrain for the elaboration of allergic phenomena In the anterior uvea a rich supply for nutrition and the formation of aqueous is insured by the anastomosing networks of the anterior and the posterior ciliary arteries, which join at the major and the minor iridic circles As a result, proteins antigens and antibodies are concentrated in the anterior uveal structures These two factors the rich vascular supply and the presence and formation of aqueous make the delicate structures of the anterior uvea a vulnerable target for sensitization by any

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choriocapillaris, which is responsible for the nutrition of the outer retinal layers The extremely abundant sinusoidal system of blood vessels almost erectile tissue, acts frequently as a sieve to trap metastatic emboli It also provides an admirable site for sensitization by circulating bacteria and antigens toxins and proteins

It has been shown by Salzmann (15) Muller (16), Schweizer (17) and Fukala (18), that the posterior uvea contains numerous smooth muscle fibers in its suprachoroidea grouped in bundles or singularly The exact role that these smooth muscles play in allergic manifestations in the uveal tract has not yet been established but their presence is important as a potential reactor organ

Perhaps much more significant from an immunologic point of view has been the discovery by many different investigators—Redslob (19) and Salzmann (15)—that the choroid contains many wandering cells which form part of the reticulo endothelial network which is present throughout the body

The reticulo endothelial system is an essential factor in defending the organism from noxious exogenous stimuli This protection is both cellular and humoral Cellular elements are elaborated at the sites of inflammation and by their phagocytic and chemotactic actions localize the offending agent The humoral response of the reticulo endothelial system is related to antibody formation It is believed (20 21) that the production of anti bodies is a specific characteristic of the reticulo endothelial system

The abundant vasculature of the uvea appears to be a factor in the local production of antibodies in situ Experiments performed by Goldmann and Witmer (22 23) have indicated that such local production of antibodies occurs in the reticulo endothelial cells of the uveal tract These authors studied the antibody formation in the aqueous of animals affected with lepto pirosis Simultaneous estimations of serum antibody formation were performed Their results indicated that in the first week following in fection the antibody level was low in the serum but nevertheless higher than in the aqueous However by the tenth day coincident with the appearance of plasma cells in the choroid the antibody content of the aqueous rises so rapidly that its concentration becomes three times as great as that of the serum This would appear to indicate that local anti body formation can and does occur in the uveal tract and that it is most likely a function of the plasma cells of the reticulo endothelial system

Experimental Evidence

The volume of animal experimentation utilizing the uvea as a shock organ is considerable Early investigators in the field of immunology recognized the advantages offered by study of this structure and a great deal of basic knowledge of generalized allergic reactions stems from this approach The application of this experimental method to the study of uveal inflammation per se was actually a by product of their work

While many of the experimental reactions demonstrated in animals have not been experimentally induced in human beings it is possible by analogy and through the study of the disease in humans to observe highly sug gestive similarities between the human disease and its experimental counterpart A brief review of some of the pertinent and salient features of the numerous experimental studies is presented in order to clarify the theories which follow

In 1908 Nicole and Abt (24) first sensitized guinea pigs to horse serum by means of intraperitoneal injections Once hypersensitivity was estab lished anterior chamber injection with the same antigen resulted in the typical picture of nongranulomatous iritis This work was subsequently confirmed and amplified by contributions of Sattler Krusius Romer and Gebb von Szily and Arisawa and others (25)

In all these experiments, however, an intraocular injection was performed. In 1916 Woods (26), using horse serum as an antigen, showed that in dogs sensitized by intraperitoneal injections without injury to the eye a constriction of the pupils occurred when the heads were perfused at a later date with the specific antigen. Small retinal hemorrhages also occurred. In later studies Woods (27) showed that in dogs sensitized by intraocular injections of an emulsion of uveal pigment later injections intraperitoneally caused allergic iridocyclitis in the other eye. Somewhat similar findings had been noted by Dold and Rados (28). Riehm (29) confirmed this in 1930, using horse serum.

In 1929 Derrick, Swift and co-workers (30) performed experiments in which they originated the term "the ophthalmic reaction." Rabbits were first sensitized by intravenous or intracutaneous injections of various proteins. Later, the sensitizing antigen was placed in the animal's conjunctival sac after corneal scarification to facilitate passage of antigen into the anterior chamber. Acute iritis devoid of any purulent characteristics ensued. The reaction did not occur in nonsensitized animals.

In 1930 Seegal and Seegal (31) succeeded in directly sensitizing the eye to horse serum and causing it to behave as a shock organ when it subsequently was exposed to the specific sensitizing antigen. This observation was confirmed by Julianelle (32). In 1933 Nectoux (33) found that when subconjunctival injections of horse serum were given to animals previously sensitized systemically to this antigen, within thirty minutes a violent ocular reaction resulted with much lid edema and iritis which lasted from seventy-two to eighty-six hours. A similar injection in a nonsensitized animal resulted in only a transient local hyperemia unassociated with any edema. When Nectoux reversed the procedure and gave subconjunctival injections of horse serum first and then followed with intravenous horse serum, the violent ocular reaction again occurred as in the first experiment.

Seegal, Seegal and Khorazo (34) in 1933 performed a series of experiments which could be considered the analogue of recurrent iritis and iridocyclitis in man. Animals were first sensitized to various proteins by intraocular injections. Many weeks later, when the eyes were once again quiescent and normal in all respects, an intravenous injection of the sensitizing antigen was given, resulting in acute iritis. These observations would appear to indicate that once sensitization has occurred in the eye it may be precipitated at a later date by a distant focus.

Another important contribution by the same investigators in 1933 (35) showed that if a nonspecific inflammation occurs in an eye at the time that a foreign protein is circulating in the blood, it is possible for the circulating protein to be absorbed directly into the ocular structures which then become sensitized to this unrelated protein. This same mecha-

nism was shown by them to explain sensitization to certain nonprotein like substances such as carbohydrates, drugs and chemicals

In a comprehensive investigation of the etiology of uveitis in 1934 Brown (36) duplicated the work of these authors and of Derrick and Swift and made further important contributions He demonstrated that streptococcal agar implants located at any site in the body could cause iritis in eyes which had been previously sensitized to the specific streptococci utilized in the agar implants We believe that this was an important step in establishing that allergic iritis may arise from an antigenic focus

Maclean (37) in 1936 caused local ocular sensitivity in untraumatized eyes by intravenous and intracutaneous injections of specific antigens In these experiments the eyes were sensitized to the antigen circulating in the blood No manipulation of any nature was used on the eyes Subsequent administration, subcutaneously or intravenously, of this same antigen produced an allergic reaction in the eyes The entire process of sensitization and shocking was achieved extra ocularly This important study has indicated that extra ocular administration of an antigen can sensitize the eye and later elicit an ocular inflammation without any direct trauma to the eye itself

The majority of the experiments described above have been directed at determining the ability of the eye to behave as a reactor site for various immunologic studies However the mechanism by which the uveal tract produces antibodies has been studied only in the past few years

Schlaegel (38) showed that injection of horse serum into one eye resulted in an allergic reaction in the contralateral eye following intravenous or intracutaneous injection He found that when the eye instead of the skin was used for sensitization the degree of reaction was much greater suggesting that formation of antibodies does take place locally The work of Witmer (39) and of Goldmann and Witmer (22) alluded to earlier bears re emphasis in this connection Working with leptospiral iritis in rabbits these authors discovered high antibody titers in the aqueous within ten days which exceeded that present in the serum by a ratio of three to one The authors concluded that the eye—probably through the uveal tract—is capable of elaborating antibody Using leptospiral antigen tagged with fluorescein Witmer (23) demonstrated its uptake by the uveal tract in large quantities in eyes which had been previously sensitized by this antigen

It would appear that the ability of the uveal tract to serve as a field for the complex interplay between antigen and antibody has been adequately demonstrated Although these observations have not been duplicated in man it can be assumed that the modus vivendi in the human is analogous This assumption is supported by similar allergic and immuno-

logic experiments carried over from the animal to the human in other related fields of allergy

Clinical Evidence

The best clinical corroboration of an allergic mechanism in uveitis is to be found in serum sickness. In this condition bilateral iritis has been observed complicating the course of generalized serum sickness in a manner entirely consistent with allergic serum reactions experimentally induced. These observations offer strong clinical indication that the eye can participate in a generalized allergic reaction to protein antigens. Other instances of uveal reactions of an atopic character have been noted to occur from pollens, animal proteins, foods and drugs and in angioneurotic edema. These observations will be discussed under atopic reactions of the uvea.

Clinical evidence for microbiallergic uveitis will be presented when that entity is discussed. The closest approximation to the experimental production of iritis in humans from the use of bacterial antigens is to be found in those sensitized patients who develop anterior uveitis following the local or systemic administration of tuberculin or BCG vaccine. Such reactions have been encountered by numerous observers.

CLASSIFICATION OF ALLERGY OF THE UVEA

On the basis of general allergic principles and our experimental and clinical knowledge of uveitis the following classification shown in table 11 is offered. This approach is a valuable aid in recognizing and differentiating the underlying allergic mechanisms operative in many of these clinical syndromes. The more important forms of uveal inflammation in which allergy appears to play a significant role will be discussed from this point of view.

TABLE 11

Classification of allergy of the uvea

1. *Anaphylactic and atopic reactions*
   Uveitis from sera, pollens, animal proteins, foods, drugs, angioneurotic edema
2. *Microbiallergic reactions*
   a. Nongranulomatous uveitis (allergy apparently the main factor): Streptococcus, tubercle bacillus, Staphylococcus, gonococcus, pneumococcus
   b. Granulomatous uveitis (allergy not primary factor but may alter the nature of the inflammatory response): tuberculosis, lues, toxoplasmosis, brucellosis
3. *Autogenous allergic reactions*
   a. Sympathetic ophthalmia (allergy to autogenous uveal pigment)
   b. Endophthalmitis phacoanaphylactica (allergy to autogenous lens protein)

ANAPHYLACTIC AND ATOPIC REACTIONS OF THE UVEA

The best examples of uveitis of atopic origin are those instances due to serum sickness and angioneurotic edema Less well documented reports have incriminated other atopic antigens such as pollens other inhalant animal proteins and foods

Reactions to Serum

As mentioned previously, the observation of iridocyclitis as a manifestation of generalized serum sickness offers important clear cut clinical evidence that the uvea may take part in allergic reactions systemic or otherwise Theodore and Lewson (40) were the first to report (in 1939) such an occurrence in a patient who had received Type I antipneumococcus serum for lobar pneumonia Later with the onset of typical serum sickness the patient developed bilateral iritis The most striking thing about the ocular process was the disparity between the extent of the intra ocular involvement and the lack of subjective symptoms other than impaired vision The anterior chamber contained a good deal of fibrinous exudate so thick that it resembled absorbent cotton yet there was only minimal inflammatory reaction and only slight discomfort Despite limiting treatment to the use of mydriatics improvement was rapid the condition cleared promptly in a week—so different from the usual course of iridocyclitis with equally extensive pathologic changes The entire picture suggested a transitory exudative reaction into the anterior chamber much like that in other synovial cavities All diagnostic tests other than reactions to horse serum were negative in this patient

In discussing the background for their conclusion that the iritis that occurred in this patient was part of the serum sickness the authors drew attention to the experimental work of Iga (41) This investigator was able to incite plastic iridocyclitis as well as large foci of choroiditis in rabbits with two or three injections of ten cubic centimeters of horse serum or on the single injection of at least twenty cubic centimeters As in the case described by Theodore and Lewson the experimental iritis produced by Iga proved mild and transitory

An even more remarkable instance of bilateral iridocyclitis due to foreign serum was reported by Sedan and Guillot (42) in 1955 Because of an unusual set of circumstances the patient developed this unique uveal reaction on three distinct occasions following the administration of tetanus antitoxin Each succeeding time the shock organ (the uvea) responded more promptly The first episode occurred in 1946 and took three days to become apparent In 1952 bilateral iridocyclitis developed ten hours after the injection of antitoxin The last episode followed the administration of the serum while he was unconscious due to an injury By the time he had

recovered consciousness ten hours later the iritis was full blown and complicated by a slight rise in intra ocular tension Skin and ophthalmic reactions to both tetanus and diphtheria antitoxins were strongly positive

In the same communication Sedan and Guillot reported other apparently allergic uveal reactions A patient had received six injections of placental extract as a treatment for cataract One year later six weeks after intracapsular cataract extraction had been performed uneventfully an abdominal implant of fresh placenta was made Four days later a severe uveitis developed which responded only when the implant was removed The authors felt that after original sensitization to placental extract through repeated injections later placental implant was responsible for an allergic reaction of the uvea Another patient developed severe bilateral uveitis following the administration of a vaccine of the cold blooded variety of tubercle bacillus (which causes disease in reptiles amphibians and other cold blooded animals) Only when the use of this product was stopped did improvement occur This would appear to be an instance of microbiallergic uveitis

Hoover (43) reported two additional instances of uveitis due to horse serum The first was unilateral, the result of tetanus antitoxin administration nine days previously Later a small intradermal injection of antitoxin resulted in focal recurrence of the iritis The other patient who developed typical serum sickness due to diphtheria antitoxin manifested bilateral anterior uveitis one month later Here too there was only little inflammatory reaction but considerable fibrinous exudation in the anterior chamber

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Reactions to Foods

Instances of uveitis due to foods are as rare as those due to inhalants according to the literature A patient with iridocyclitis which subsided following the removal of egg and chicken from the diet has been described by Parry (51) In his report he describes the direct causal relationship between exposure to these foods and the exacerbation of the strongly positive skin reactions to egg white and to chicken Uveitis due to allergy to eggs is also mentioned by other authors (48 52)

Angioneurotic Edema of the Uvea (Quincke's Disease)

Involvement of the uvea in the course of angioneurotic edema was emphasized by Weekers and Barrac (53) in 1937 under the title of Allergic Paroxysmal Intraocular Edema Their patient had had his right eye enucleated He was seen one year later because of symptoms in the left eye similar to those leading to enucleation of the other eye These consisted of iridocyclitis with elevated tension, for which an iridectomy was performed Following this several episodes of generalized angioneurotic edema occurred in which the eye itself was involved with ciliary injection edema of the cornea iritic hemorrhages cloudy media and slight elevation of tension

Potvin and Bossu (52) have listed a number of other instances of involvement of the anterior portion of the eye in angioneurotic edema In many of these only the cornea was affected not the uvea

Hambresin (54) described a classical instance of recurrent bilateral uveitis associated with other widespread manifestations of angioneurotic edema His patient had frequent episodes of edema of the lower lip and left breast which were usually followed by ocular involvement consisting of corneal edema iridocyclitis and elevated intra ocular tension Hambresin felt that the sequence of events that always took place the preliminary generalized manifestations followed by the ocular complication were part of the same allergic angioneurotic process The patient s dramatic response to antihistaminics confirmed this diagnosis in Hambresin s opinion

We have observed a patient with recurrent unilateral edema of the eyelids associated with severe anterior uveitis accompanied sometimes by an increase in intra ocular tension On two occasions in addition to the edema the uveitis and the increased tension four to five millimeters of exophthalmos were also present Since all etiologic investigations were negative it is possible that this patient falls into the category of paroxysmal allergic edema even though no allergen has been demonstrated As noted in chapter 11 in many instances of angioneurotic edema and urticaria the actual causation is never demonstrated

MICROBIALLERGIC REACTIONS OF THE UVEA

Microbiallergic Uveitis Due to the Streptococcus

Most instances of nongranulomatous endogenous uveitis in which bacterial hypersensitivity plays an etiologic role appear to be due to the streptococcus. The almost uniform failure to demonstrate viable organisms in uveitis indicates that if foci of infection contribute in any way to the causation of the condition it is not by direct organismal spread.

The paucity of findings in the aqueous when it is examined during the height of an attack of iridocyclitis is well established. In 1931 Kolmer (55) demonstrated that cultures made from aqueous withdrawn from the anterior chamber during the height of an attack were invariably sterile. Repeated attempts to isolate infective agents in the aqueous by Von Sallmann *et al* (56), Berens *et al* (57), Brown (36) and Braley (58) who also made attempts to isolate viruses from the aqueous were all unrewarding. Amsler and Verrey (59) however discovered organisms in the aqueous during attacks of the iridocyclitis in a very small percentage of patients but as Woods (11) indicated it is likely that these were dead on arrival bacteria or else conjunctival contaminants. These findings have not been duplicated by other observers employing similar techniques for aqueous analysis. The experimental evidence in man indicates that anterior uveitis is unassociated with any local bacterial infection.

The antigenic properties of the Streptococcus. Immunologic evidence implicating the Streptococcus as a cause of allergic nongranulomatous uveitis is based upon our increasing awareness of the important antigenic characteristics of the Streptococcus and its products.

Numerous classifications of the streptococci have been propounded but the only two which have been generally accepted by microbiologists are those of Smith and Brown and of Lancefield.

Smith and Brown have divided the streptococci into three main groups according to their effect on blood agar plates.

Alpha. In this group known as the *Streptococcus viridans* are included all strains which produce a greenish discoloration and partial hemolysis of the blood agar plate in the immediate vicinity of the colony. Examples are the *Streptococcus viridans*, *Streptococcus bovis* and *Streptococcus equinus*. They are on the whole not pathogenic for man.

Beta. This group produces completely clear hemolyzed zones on the blood agar surrounding the colonies. This is known as the hemolytic group and contains most of those microorganisms pathogenic for man. Examples are the *Streptococcus pyogenes* and *Streptococcus scarlatinae*.

Gamma. This group produces no change (hemolysis) whatsoever in the blood agar plate in the vicinity of the colonies and is referred to as the

Streptococcus anhemolyticus Important examples are the *Streptococcus lactis* and the *Streptococcus fecalis*

By means of specific precipitin reactions to the group C carbohydrate fraction of the Streptococcus organism Lancefield has further subdivided the beta hemolytic group into twelve subgroups A through N Group A contains most of those streptococcal organisms which are known to be pathogenic for man Each subgroup can be further subdivided on the basis of two type specific antigenic protein fractions called the M and T substances both of these have specific individual characteristics It is believed *that the M antigen is closely related to the virulence of the Group A* streptococci The T antigen is connected with the agglutination reaction and is of considerable importance since it is the most powerful antigen thus far extracted from streptococcal cells

In addition to the C group polysaccharide and the M and T antigens a group of nucleoproteins designated as the P substance are also capable of elaborating antibodies

Besides these somatic antigens elaborated by the Streptococcus these

tokinase factors

Evidence for streptococcal allergy *The anti streptolysin titer* The anti streptolysin titer is a measure of the circulating antibody to specific extracellular hemolysins which are elaborated by the Streptococcus While the Streptococcus elaborates many antigenic fractions the anti streptolysin titer is easily measured and is considered to be the most reliable index of recent or current streptococcal infection Elevation of the anti streptolysin titer in patients with nongranulomatous uveitis above that of a control population would be presumptive evidence that recent streptococcal infection had occurred in these patients

Leopold and Dickinson (60) have indicated that serum titers for anti streptolysin were higher in patients with nongranulomatous uveitis than in a control group of normals Steen and Schone (61) measured the anti streptolysin and the anti staphylococcus level in patients with iridocyclitis and *a normal control group of patients* excluding all of those with a previous history *of infection The results of the anti staphylococcus titers* were the same for both groups However the anti streptolysin titer was on the average 35 units higher in patients with iridocyclitis The authors claim that this is a significant figure Smith and *Ashton (62) were able* to corroborate substantially the finding of an elevated anti streptolysin titer in patients with nongranulomatous uveitis

Skin testing Woods (63) has demonstrated by means of intradermal

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An evaluation of desensitizing procedures as applied to uveitis is rendered difficult due to the occurrence of spontaneous exacerbations and remissions in the natural course of this variable disease An important drawback in judging the efficacy of specific desensitization is the difficulty of establishing suitable controls

Although little is known of the exact pathogenesis of uveitis the most significant and important laboratory finding which implicates the Streptococcus in nongranulomatous uveitis has been the discovery of elevated anti streptolysin titers in patients with nongranulomatous uveitis This is *prima facie* evidence that these patients have recently suffered from some streptococcal disease It is therefore suggestive though not certain that there may be some relationship between a recent streptococcal infection and nongranulomatous uveitis

While little has been definitely established concerning the exact mechanism of nongranulomatous uveitis there is much suggestive experimental and clinical evidence supporting the assumption that the pathogenesis of uveitis is most likely linked to streptococcal hypersensitivity The precise tools and quantitative methods necessary to establish this concept with certainty are lacking at present However our own as yet unpublished studies in this field indicate that serial anti streptolysin titers in patients with all types of uveitis as well as in normal controls show no significant differences

Nongranulomatous Uveitis Due to Other Bacterial Antigens

Gonococcus The importance of chronic gonococcal infections in the causation of anterior uveitis recognized by clinicians many years ago has now waned with better control of venereal diseases in general There appears to be no question that bacterial allergy not direct bacterial in

products It is noteworthy that focal ocular reactions to streptococcal antigens are exceedingly rare

Other pitfalls in the interpretation of skin tests stem from the nature of the skin being tested and from nonspecific ingredients of the test solutions Patients with fair skin and light or red hair show more intense reactions than do brunettes (65) Aged persons with atrophic skin may give sluggish reactions even in instances of high sensitivity Cutaneous phenomena may also be affected by the amount of local histamine in the skin as well as by the amount of circulating inhibiting drugs such as epinephrine corticosteroids and antihistamines (65)

Misleading nonspecific skin reactions are not uncommon Some skins will react to any intradermal injection of particulate matter On occasion irritants introduced in the preparation of the product used may cause reactions Thus in skin testing with heat killed streptococci the reaction elicited may at times be due entirely to the particulate nature of the organism apart from its specificity and may give rise to false positive results

Determining the specific antigenic fraction to which the patient is sensitive is complicated by the complex antigenic mosaic of which bacteria are composed As many authors have indicated the carbohydrate and nuclear protein fractions may produce different immunologic reactions which often bear no relationship to their specific infective characteristics Experiments confirming this were performed by Avery and Tillett (66) who were able to sensitize guinea pigs passively with rabbit antipneumococcus serum and then elicit fatal shock in these animals by injecting the type specific carbohydrate of the pneumococcus Mackenzie (67) sensitized animals to killed or living broth cultures of virulent pneumococci producing active immunity and then induced fatal anaphylactic shock with intravenous injections of pneumococcus filtrate Tillett and Francis (68) have verified this phenomenon

The exact clinical significance of positive skin reactions to streptococcal antigens is subject to varying interpretations

Lawrence (69) has found that positive skin reactions to different streptococcal fractions occur in a relatively large segment of a random hospital population His study indicates that in a group of four hundred and seventy two patients eighty eight per cent exhibited positive skin reactions to streptococcal materials When he eliminated the equivocal plus minus and plus reactions from this group he still found that two hundred and twelve or forty five per cent gave definitely positive skin reactions It is generally accepted that in the population at large the incidence of positive reactions to streptococcal products increases with the age of the population

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vasion is the inciting factor The especial value of foreign protein therapy and hyperpyrexia is strong evidence in this regard Gonococcal complement-fixation tests while of debatable significance nevertheless are almost regularly positive in such cases and are certainly suggestive as to the etiology Gonococcal antigens give markedly positive reactions on intradermal injections It must be stressed that even in this antibiotic era any particularly severe plastic anterior uveitis should alert the ophthalmologist to the possibility of gonococcal origin of the iritis especially if the history or general examination offer clues of this nature

Other bacteria Less often other bacteria may evoke nongranulomatous uveitis on an allergic basis These include *Pseudomonas aeruginosa* (*B pyocyaneus*) (11), and pneumococcus (where the evidence suggests specific polysaccharides as the responsible antigens), coliform organisms (70) and rarely the Staphylococcus De Argumosa (71) has reported an interesting instance of allergic iritis due to the latter organism which according to him cleared dramatically on treatment with staphylococcal vaccine Dworetzky (72) has reported an instance of bilateral uveitis presumably due to staphylococcal allergy The patient exhibited marked immediate and delayed reactions on skin testing to Staphylococcus products and developed a focal reaction characterized by acute uveitis and optic neuritis Although treatment included surgical extirpation of a focus containing pathogenic organisms and systemic corticosteroids it was the author's opinion that desensitization with vaccine therapy contributed materially to the ultimate subsidence of the condition

The Role of Microbial Allergy in Granulomatous Uveitis

As has been noted previously even in those forms of granulomatous uveitis where direct organismal invasion occurs the inflammatory reaction may be modified by local tissue hypersensitivity In fact on occasion the allergic reaction may be so intense that the true infective nature of the process may be masked In certain forms of granulomatous uveitis due to microorganisms such as tuberculosis toxoplasmosis and apparently brucellosis the allergic component appears to be of particular importance in influencing the clinical picture Moreover in at least one form of granulomatous uveitis (tuberculosis) it is believed by some that at times allergy may be the sole precipitating factor and that no direct infection of the uvea need occur Even in syphilitic uveitis allergy may be of some significance as indicated in part by Herxheimer reactions and responses to steroid therapy

Tuberculosis The once dominant role ascribed to tuberculosis in the etiology of uveitis has with the increase of our knowledge in this field undergone considerable de emphasis The advent of such potent anti

tuberculostatic drugs as streptomycin, para-aminosalicylic acid, and the isoniazids has made possible a specific therapeutic test resulting in greater precision in diagnosing uveal tuberculosis. This, coupled with greater accuracy in recognizing other important entities such as toxoplasmosis (especially the adult variety), brucellosis, and sarcoid, have led to a downward revision of the statistical incidence of uveal tuberculosis. This change is reflected by newer statistical studies. In 1941 a report (6) from the Wilmer Institute indicated tuberculosis to be the cause of seventy-nine per cent of all instances of uveitis. In 1944 (7) this figure had dropped to fifty-two per cent, and in 1953 to twenty-three per cent (73), a drop at this institution of over fifty per cent in about a decade. The present-day concepts of the importance of tuberculosis as a cause of uveitis vary considerably. Thiel (74) in 1953 found that in Germany the incidence of tuberculous uveitis was seventy-five per cent. On the other hand, Amsler (75) in nearby Switzerland stated that in only ten per cent of patients with uveitis could he be certain of a tuberculous etiology.

In a controlled study, Hanno and Spaeth (76) found that in a six-year period the uveitis population of the Wills Eye Hospital in Philadelphia did not exhibit a higher incidence of positive reactions to tuberculoprotein than did a control series.

The incidence of ocular tuberculosis is not proportional to the incidence of the systemic disease. Ocular involvement rarely occurs in systemic tuberculosis unless there is miliary dissemination. A study by Fritz *et al.* (77) of 2,000 Alaskan children, all of whom were afflicted with pulmonary or extrapulmonary tuberculosis, failed to uncover a single instance of uveitis, tuberculous or otherwise.

It seems to us that the lack of correlation of eye complications with systemic tuberculosis might indicate: 1) that a long latent period occurs before the tubercle bacillus travels from the lung or any extrapulmonary source to the eye; 2) that the uvea is not an especially receptive site for the *Mycobacterium tuberculosis*; or 3) that some other mechanism (possibly allergic) is responsible for uveal tuberculosis.

In tuberculosis an unusually good opportunity exists to study the relationship between allergy and immunity. The classical example of this relationship is the well-known Koch phenomenon. In guinea pigs given subcutaneous injections of tubercle bacilli in the thigh, Koch found that the original puncture wound healed within two days but then broke down within ten to fourteen days, forming an indurated ulcer which did not heal. The regional lymph nodes underwent caseation necrosis. If a few weeks later the opposite thigh of the same animal was similarly injected, a small indurated nodule appeared within twenty-four to forty-eight hours and then ulcerated. In contradistinction to the first injection, the ulcer then

healed without regional lymph node caseation Koch later elicited the same reaction with heat killed bacilli by injecting a filtrate of heated tubercle bacilli (tuberculin) Two conclusions can be drawn from these findings 1) that the animal developed a hypersensitivity to the tubercle bacilli and 2) that it developed the ability to localize the infection Thus both allergy and acquired immunity had developed

The relationship between allergy and immunity is difficult to evaluate Some investigators believe that they are closely related and perhaps identical others consider them to be entirely distinct and opposing reactions

The balance between allergy and immunity determines the nature of the host's response to viable tubercle bacilli whether primary infection or reinfection Rich (78) has expressed this in a formula He states that the severity of the lesion is determined by the virulence number of infecting organisms and the allergy present counterbalanced by the resistance of the host This formula accounts for the tremendous pleomorphism of all tuberculous lesions The nature of the lesion in a young highly susceptible adult in whom extreme hypersensitivity develops during the course of infection is quite unlike that found in a young adult who was primarily infected in childhood and who after a period of years has developed a great deal of immunity together with hypersensitivity This second individual will rapidly wall off and contain the ocular lesion after an initial vigorous inflammatory reaction If at a later date his immunity should decline it is quite likely that the lesion will reactivate into a low grade chronic inflammation In the choroid such reactivation is indicated by *satellite areas of choroiditis appearing along the borders of the old lesions*

The ability of the uveal tract to react allergically to soluble fractions of the tubercle bacillus without actual tissue invasion or proliferation of the organism is well known The uvea can be sensitized to circulating tubercle bacilli living or dead or to their soluble products Thereafter the eye can react allergically to circulating moieties of the bacillus

Ashton (12) has recently refocused attention on the concept that hypersensitivity reactions in the uvea can result from some extraocular form of tuberculosis He leans to the older belief that tuberculous uveitis may often occur on an allergic basis instead of being the result of direct organismal invasion He finds the tuberculin test to be positive more often in acute anterior uveitis than in chronic posterior uveitis

It is our opinion that not only may acute anterior uveitis arise on the basis of allergy to products of the tubercle bacillus but that posterior uveitis of the granulomatous variety may similarly occur without bacterial invasion

The value of the Mantoux test in ocular tuberculosis is debatable A positive Mantoux merely indicates past exposure to tuberculosis (usually pul

monary), and does not of itself prove that the uveitis is of tuberculous etiology. If the uveal tract is invaded by the tubercle bacillus this infection is generally secondary to a focus elsewhere in the body. Although the eye can serve as a port of entry for the tubercle (79) this is not a frequent occurrence. Therefore, the information regarding the eye gained from a positive tuberculin reaction in a person with uveitis is of somewhat dubious value. The prevalence of positive Mantoux tests in the western part of the world further detracts from the value of this test. The previously mentioned study of Hanno and Spaeth is pertinent in this connection. Moreover, there is evidence that the Mantoux reaction can become negative spontaneously, although this is not common. Woods has shown that ocular sensitivity can be high and at the same time cutaneous sensitivity low so that correlation between the results of skin testing with tuberculin and ocular sensitivities is of a low order. However on those rare occasions when focal reactions occur in the eye following intradermal injections of tuberculin, the diagnostic significance is apparent.

Reactions during therapy. Varying reactions occurring in the course of the treatment of uveal tuberculosis are of interest from the point of view of etiology. For this reason they will be discussed briefly at this point. Treatment will be discussed in detail at the end of the chapter.

The therapy of tuberculosis of the uveal tract is based on three principles: 1) enhance the host's natural immunity, 2) decrease the host's hypersensitivity, and 3) destroy the bacilli.

Nonspecific methods consisting of proper environment, rest, enriched diet and the general welfare of the patient are time honored means of enhancing natural immunity in tuberculosis.

Decrease in tissue allergy is accomplished through desensitization with tuberculin in gradually increasing doses. This procedure, though advocated by Woods (11) in this country, is not employed too commonly because of the evident danger of reactivating a focal lesion in the eye which is already damaged by uveal tuberculosis. Reports of the danger of reactivating ocular foci with tuberculin are numerous and are mentioned by Rich (78), Duke-Elder (80), Wessel (81) and Choyce (82). Great caution must be employed in instituting desensitization with tuberculin and the results achieved are frequently open to question. Rich gives hesitant approval to the procedure, emphasizing the dangers inherent in this form of therapy and the comparatively poor results which are obtained. The long period of time necessary to obtain partial desensitization, the almost immediate return of tissue allergy (if any loss had occurred) following the cessation of therapy, and the extreme danger of reactivating a focal lesion make desensitization a dangerous, tedious and unrewarding method of treating tuberculosis of the uveal tract. Seegal (83) has reported that

the results of desensitization are temporary, once the injections are discontinued the patient usually reverts to his previous state of hypersensitivity Choyce (82) has indicated that desensitization with tuberculin is rarely used in Europe for either ocular or systemic tuberculosis The same situation prevails in the United States at this time

The introduction of such potent antitubercular drugs as the isoniazids para aminosalicylic acid and streptomycin has revolutionized tuberculosis therapy Destruction of viable and antigen producing tubercle bacilli automatically halts the progress of proliferating and caseating tissue destruction and at the same time the production and liberation of antigen is curtailed However treatment with so called specific measures may be followed by adverse effects Thus Borioni (84) found that treatment of extraocular forms of tuberculosis with streptomycin might result in severe ocular disease consisting of conjunctivitis acute iridocyclitis plastic uveitis or phlyctenular keratitis When therapy was discontinued the adverse reaction subsided It would appear that the effect of streptomycin on the tubercle bacillus is to liberate antigen through destruction of the bacteria leading to sensitization of the ocular structures This report would seem to indicate that destruction of the tubercle bacillus results in reactions of the Herxheimer type such as are encountered in antiluetic therapy

Choyce emphasized that failure to respond to the therapeutic test in instances of known ocular tuberculosis does not necessarily indicate an incorrect diagnosis Instead it suggests that these are patients in whom the tuberculosis is predominantly of the allergic type the tubercle bacillus invasion being minimal or absent

Toxoplasmosis Interest in toxoplasmosis as a cause of adult uveitis was slight prior to Wilder s report in 1952 (85) of the histologic demonstration of *Toxoplasma gondii* in the chorioretinal lesions of 52 adult eyes enucleated because of pain and blindness and diagnosed clinically as tuberculous uveitis A few reports suggesting that this organism might play an important role in the causation of adult uveitis had appeared previously Frenkel (86) had found a definite correlation in a small group of hospital patients between cutaneous reactions to Toxoplasma and uveitis

Wilder s report led to renewed interest in the potentialities of this organism as a cause of adult uveitis Woods (73) re examined a series of cases from the Wilmer Institute and performed dye tests on their old frozen sera He estimated that toxoplasmosis could account for as much as twenty-five per cent of granulomatous uveitis in these patients Ryan and his group (88) estimated that twenty nine per cent of adult uveitis was due to toxoplasmosis and that twenty per cent responded to specific therapy directed against the Toxoplasma Jacobs Fair and Bickerton in

1954 (89) presented the first parasitologically proven case of adult toxoplasmic uveitis in the United States In addition to their important report Habegger (90) in Switzerland has described two more instances of adult toxoplasmic uveitis in which the organism was isolated

Toxoplasmosis may appear in two forms, congenital or acquired both may exhibit ocular manifestations The congenital variety is more commonly encountered and has been better documented It is passed on to the fetus through the placental circulation and the newborn child usually exhibits all or some of the characteristics of the disease cerebral calcification, hydrocephalus, retarded mental development, occasional splenomegaly or hepatomegaly and bilateral chorioretinitis The ocular lesions consist of a focal chorioretinitis usually involving the macular area but sometimes affecting the more peripheral retina These lesions are characterized by their regular and dense accumulations of pigment surrounding a central zone of atrophy through which the white sclera may be seen Often associated with the chorioretinitis there is nystagmus strabismus and in some instances, microphthalmos In most instances the parasite localizes in the retina, not the choroid There is no organismal invasion of the choroid, which is involved by an extension of the inflammatory reaction from the infected retina The organisms are present in the retina in the self-elaborated pseudocyst form and, as such can liberate little antigen for antibody stimulation

Acquired toxoplasmosis is a common disease and the results of serologic testing indicate that the incidence varies considerably from area to area In temperate climates positive dye tests are obtained in thirty to sixty per cent (91) of the adult population The acquired form manifests itself in four clinical types 1) an exanthematous variety 2) a central nervous system variety, 3) an afebrile lymphadenitic form, and 4) an ophthalmic form

In the ophthalmic form the symptoms appear to be limited essentially to the eye and consist of a uveitis which is usually unilateral The course is that of a granulomatous type of disease The lesions, while basically similar to those seen in the congenital variety, are encountered in the active phase In the adult the diagnosis as in practically all instances of uveitis, must be a presumptive one based upon clinical evaluation the exclusion of other presumptive diagnoses and, most important, the Sabin-Feldman cytoplasm modifying antibody dye test Initially, in the acute stages of the disease, a paracythemia exists but is difficult to demonstrate The complement fixation test is too fleeting to be of practical value The skin test is of value only when it is positive The dye test titers, unless they are rapidly changing are no indication of the acuteness of the disease Hogan (87), on the basis of the low antibody titers to the Toxoplasma in

patients with uveitis, considered it unlikely that this was a common cause of uveitis However, in a later communication (92) he found that while the dye titers in patients of all ages with chorioretinitis were low they were nonetheless significantly higher than in a control group of patients without chorioretinitis Hogan postulated the existence of strains of Toxoplasma of low antigenicity which are capable of producing a severe uveitis without stimulating the production of antibody

The exact evaluation of dye titers in relation to adult toxoplasmic uveitis is not entirely clear In the patient with proved ocular toxoplasmosis reported by Jacobs Fair and Bickerton (89) marked fluctuations in this test were observed Their patient afflicted with recurrent uveitis of eight years duration exhibited a dye titer of 1 64 before enucleation Immediately following surgery this rose to 1 4096 and later it fell to 1 128 These findings would seem to indicate that the value of the dye test rests on a qualitative rather than a quantitative basis Smith and Ashton (62) assessing the results of the dye test in a patient suspected of having toxoplasmosis stated that it is perhaps necessary to consider several dye tests before attaching any particular significance to the results particularly because of the frequency of positive dye tests in the adult population at large The ability of the host to produce specific antibodies to the toxoplasma varies A low dye titer might be explained on the ground that when the Toxoplasma becomes localized in the eye this organ behaves as a separate and walled off structure so that systemic antibody production is low This could account for the low titers occurring in patients with suspected toxoplasmic uveitis The possible relationship between encystment and low antibody titers has been mentioned above In the active phase when the organism becomes extracellular the antigenic response would depend solely on the number of organisms liberated If few are liberated the stimulus to antibody formation would be low

Allergy in toxoplasmic uveitis There is some evidence that the role of allergy in the production of the actual uveitis may eventually be shown to be an important one Since the condition is predominantly a retinal disease the choroidal inflammatory response is directed against toxins or antigens not the infecting organism itself Whether the process is associated with any important degree of local hypersensitivity is conjectural Frenkel and Friedlander (93) have suggested that the ocular tissues are first infected with the organism which forms pseudocysts of the retina Both local and general sensitization occur the latter manifested by low positive dye titers When the pseudocysts rupture perhaps years later the sensitized tissue reacts with the liberated organisms to produce an allergic reaction clinically manifested as uveitis Sabin (94) considers that congenitally acquired toxoplasmosis may be the cause of ocular in

flammation in adult life He feels that there is strong support for the concept that adult ocular toxoplasmosis may represent an allergic inflammatory response to ruptured pseudocysts

While steroids may, in a sense be therapeutically indicated as discussed later, their deleterious effect on the experimentally infected animal suggests a mechanism for the transmission of the congenital form of the disease In the laboratory-induced disease administration of steroids results in an overwhelming infection It is generally accepted that toxoplasmosis is transmitted from the mother to the fetus It is assumed that the mother contracts the disease during pregnancy and infects her child but remains, herself, asymptomatic However it might be postulated that the mother contracts the disease long before her pregnancy and then during pregnancy with its augmented steroid production the silent pseudocysts rupture and infect the fetus

SYMPATHETIC OPHTHALMIA

Sympathetic ophthalmia a disease of now declining incidence has always challenged the ophthalmologist because of its unpredictable appearance its variable (but frequently fulminating) course and its enigmatic etiology and pathogenesis Its importance is augmented in the physician's mind because of the choice between removing a wounded eye or leaving it with the attendant danger of inciting a sympathetic inflammation of the fellow eye at a later date Etiologic theories abound almost all may be classified as either infectious or allergic

The oldest is the infectious theory which was first enunciated by Berlin (95) in 1880 and vigorously championed a few years later by Deutschmann (95) Its adherents through the years have been Arlt Snellen Leber Samuels and more recently Schreck (96) The basic tenet is that a bacterial viral or a rickettsia like organism is present as a saprophyte upon the conjunctiva or the cornea When a perforating wound of the globe occurs these organisms are driven into the eye and upon contact with the uveal tissues become pathogenic They set up an inflammatory reaction which terminates usually by migration along the course of the optic nerve in sympathetic inflammation in the other eye The criticisms of this theory are self evident Most important no organism has been discovered with any regularity in eyes with sympathetic ophthalmia The organisms reported by some observers have not been found by others Inoculation experiments have failed to reproduce the disease Furthermore it would require some entirely different mechanism to explain the rare sympathetic ophthalmia which may occur without perforation of the globe as in melanosarcoma or following severe contusion

An allergic pathogenesis appears to offer the best explanation for the

disease available at present The first suggestions in this direction are those of Calonne, which appeared in 1905 (95) He believed that injury of the ciliary body liberated toxic substances which entered the blood stream and precipitated the uveal reaction in the fellow eye

In 1910 Elschnig (9) published a series of papers which were fundamental in establishing the concept of autogenous ocular allergy and anaphylaxis Elschnig produced anaphylaxis in guinea pigs sensitized with emulsions of uveal pigment Having demonstrated the importance of uveal pigment as an antigen Elschnig assumed that a perforating injury to the eye caused uveal pigment to be liberated into the blood stream producing a generalized state of hypersensitivity in the individual Further liberation and dissemination of uveal pigment from the inciting injured eye caused an allergic inflammation to occur in the now sensitized fellow eye To Elschnig this theory seemed to explain both the variable incubation periods (sometimes decades) of the disease and the absence of bacteria

Important impetus to the acceptance of this highly original and novel concept was provided by the extensive contributions of Woods (26 27) In 1921 this investigator (97) demonstrated a specific antibody to uveal pigment in the blood of patients with perforating ocular wounds Using uveal pigment as the antigen for an intradermal sensitivity test Woods showed further that true hypersensitivity to uveal pigment occurred only in patients who had suffered a perforating wound involving the uveal tract (98)

Friedenwald (99) added substantial evidence utilizing histologic studies on the skin of individuals who had received intradermal injections of suspensions of uveal pigment Study of these sections revealed that where positive reactions occurred the area was heavily infiltrated with epithelioid and giant cells which had engulfed the pigment granules to such an extent that no free extracellular pigment was present The surrounding tissues exhibited intense perivascular round cell infiltration The pathologic picture was similar to that found in sympathetic ophthalmia In patients with negative skin reactions large amounts of free, unphagocytosed pigment and an absence of giant and epithelioid cells were noted Friedenwald felt that the uveal pigment granules acted as a specific antigen and that the disease was primarily allergic in nature

Contralateral uveitis simulating sympathetic ophthalmia has been successfully produced in experimental animals usually with horse serum after sensitizing one eye only This has been done by Woods (27), Dold and Rados (28), Riehm (29) Schlaegel and Wilson (38) and others

Collins (100) in 1949 produced lesions in the choroid of guinea pigs which histologically simulated the picture of sympathetic ophthalmia He achieved this by sensitizing the animal to intraperitoneal and intramus

cular injections of guinea pig uveal emulsion along with Freund type adjuvants (aquaphor and mineral oil plus heat killed tubercles) In later experiments he discovered that if he omitted the tubercles the typical picture failed to develop However when nonpathogenetic mycobacteria were substituted he elicited the sympathetic ophthalmia like choroidal reaction

Osterlind (101) observed that subconjunctivally injected horse serum failed to enter the aqueous unless there was associated trauma However he was able to sensitize eyes to horse serum with subconjunctival injections plus saline and to precipitate an acute iritis What is interesting was that iridocyclitis resulted when saline was omitted and instead the eye traumatized The author felt that an analogous phenomenon is present in human eyes in which sympathetic ophthalmia develops

In addition to experimental evidence the histologic findings in sympathetic uveitis suggest that the process might be allergic The granulomatous process is characterized by the presence of large numbers of round cells and lymphocytes plasma cells and giant cells In addition in contradistinction to other granulomatous processes characteristically large numbers of eosinophiles occur

Elschnig s proposal that the pathogenesis of sympathetic ophthalmia is allergic has been enhanced through the years while various other concepts have been found wanting The evidence in favor of an allergic theory of sympathetic ophthalmia has been summarized by Collins (100) as follows 1) the time interval between the initial injury and the appearance of the disease in the contralateral eye corresponds to the sensitization period as found in other immunologic procedures 2) the histopathologic picture points to an allergic process 3) Elschnig Woods and others have shown that uveal pigment can act as an antigen 4) that allergy to pigment exists has been demonstrated by bleaching of the eyelashes leukodermic patches and deafness through involvement of the pigment cells of the inner ear 5) Friedenwald has reported a case of sympathetic ophthalmia which healed spontaneously—microscopic examination revealed that the choroid had been replaced by scar tissue and that there was no remaining pigment 6) the presence of eosinophiles points to some factor of allergy

The efficacy of steroids in the control of the disease offers strong additional evidence in this direction, since these agents are particularly useful in allergies

It thus appears that allergy to uveal pigment plays a dominant role in the etiology of sympathetic ophthalmia However this concept fails to explain the entire picture clinical as well as pathologic In view of the frequency with which the iris is traumatized in intraocular surgery and in accidental trauma it is surprising that sympathetic uveitis is not en

countered more frequently—since it would be logical to assume that sensitivity to uveal pigment would occur in many such patients Other unknown factors may trigger the reaction once hypersensitivity is established The e might include the actual perforation itself or the participation of nonpathogenic conjunctival bacteria acting as adjuvants

ENDOPHTHALMITIS PHACOANAPHYLACTICA

Endophthalmitis phacoanaphylactica classically described by Verhoeff and Lemoine (102) in 1922 is similar to sympathetic ophthalmia in that it is caused by a native or autogenous protein The disease consists of a severe allergic reaction in individuals sensitized to lens protein which had entered the anterior chamber as the result of surgery, trauma or the altered permeability of a diseased lens capsule Classically, the full blown picture occurs when after an uneventful extracapsular cataract extraction a similar procedure is performed on the fellow eye in a patient now allergic to lens protein

Phacoanaphylactic uveitis is usually *restricted to the anterior* segment of the globe and consists essentially in an inflammatory reaction about disintegrating portions of lens substance in the anterior chamber The in*flammatory reaction consists of lens fibers morgagnian droplets or* lens nucleus intermingled with and surrounded by polymorphonuclear leukocytes undergoing disintegration This abscess becomes walled off by a *zone of granulation tissue consisting essentially of epithelioid cells* in a fibrovascular zone surrounded by plasma cells and lymphocytes The major cellular nourishment for this nidus comes from the richly vascular iris and *ciliary body Lymphocytic infiltration may occur in the limbic* episcleral vessels and tissues the choroid the retina and the optic nerve head However the e structures may be only very mildly involved in the disease

That the cau e of the disease is probably allergic has been accepted ever since its original discoverers named it and indicated the importance of sensitivity to lens protein as a causative *factor*

DeVeer (103) pointed out that if the lesion is to be considered an allergic phenomenon then the lens material may be regarded as a visible recognizable etiologic factor (antigen) *comparable to the melanin found* in the lesions of sympathetic ophthalmia or in the positive *Friedenwald skin* reaction

Hanser (104) reported his findings *in a patient who four weeks* prior to observation underwent an extracapsular cataract extraction On the first day of observation an anterior chamber puncture revealed an eosinophilia of thirty two per cent *Following this puncture* the residual cortex was evacuated from the anterior chamber Four days later the anterior

chamber puncture revealed sixteen per cent eosinophiles; ten days later there were only two eosinophiles in one hundred and nineteen cells. The high eosinophilia that the author reports suggests an allergic mechanism.

Burky (105) succeeded in reproducing the pathologic picture of endophthalmitis anaphylactica in rabbits by first sensitizing animals to staphylococcus toxin and lens substance. When cutaneous sensitivity had been established by needling the lenses in these animals he succeeded in producing pathologic changes in the operated eye which resembled endophthalmitis anaphylactica. Burky felt that his experiment indicated that the disease was allergic in nature.

Irvine and Irvine (106) have demonstrated that actual rupture of the lens capsule is not required for the appearance of this disease. Increased permeability of the lens capsule may result in a similar reaction. They described two interesting conditions which they called respectively phacotoxic reactions (iritis) and phacogenetic glaucoma. In both of these conditions lens substance escapes into the anterior chamber through the diseased but intact lens capsule in eyes with cataracts giving rise in the first instance to severe uveitis and in the second to glaucoma. They believe that this reaction is another type of phacoanaphylactic endophthalmitis. Although less severe the histologic findings in their patients were the same. They consider that these are allergic reactions to lens protein.

Kronenberg (107) reported four instances of what he calls sympathetic lens induced uveitis in the unoperated eye of patients who had previously undergone extracapsular cataract extraction in the other eye. Removal of the cataract in the inflamed eye in three of these patients resulted in the prompt subsidence of the uveitis. A permeable lens capsule in individuals sensitized by previous cataract surgery was apparently the basis of the uveitis. These observations would apparently substantiate Irvine and Irvine's concept of phacogenetic uveitis.

Courtney (108) indicated that endophthalmitis phacoanaphylactica could be a bilateral disease when he reported seven instances of bilateral inflammation following extracapsular cataract extraction without trauma to the second eye. In all seven patients he was able to demonstrate cutaneous sensitivity to lens antigen. A pathologic report of the enucleated second eye revealed the findings of endophthalmitis anaphylactica.

DeVeer (103) also described bilateral endophthalmitis anaphylactica which he felt was often erroneously confused with sympathetic ophthalmia.

A recent finding by Agarwal and Mehra (109) is of interest. The authors found that in one hundred cases of senile mature cataract the cutaneous sensitivity to lenticular protein extract correlated well with the cutaneous sensitivity to cysteine. Extracapsular cataract operations performed on patients with high sensitivity to lens protein or cysteine were followed by

a very marked iridocyclitis They concluded that cysteine is a probable factor in the antigenic inflammation and that cysteine sensitivity plays an important role in endophthalmitis anaphylactica

Since endophthalmitis phacoanaphylactica is an allergic disease and one which can be bilateral, deVeer (103) suggests that certain precautions should be taken in patients in whom this disease is suspected He suggests the following 1) skin tests for sensitivity to lens protein and uveal pigments should be performed in all cases of severe or prolonged postoperative or post traumatic uveitis, 2) in instances of positive skin reaction the lens in the inflamed eye should be removed as promptly and as completely as possible since in the presence of a disintegrating lens, attempts at desensitization are woefully inadequate and will fail to control the inflammation 3) in instances of unilateral endophthalmitis phacoanaphylactica following cataract extraction if surgery of the fellow eye is contemplated *desensitization is indicated unless an intracapsular cataract extraction can* be guaranteed 4) the pathologist s report of endophthalmitis anaphylactica in the enucleated eye of a patient whose second eye has become inflamed would indicate a defective lens capsule in the second eye for which prompt lens extraction is necessary, 5) the development of inflammation in a second eye with a simultaneous or slightly preceding exacerbation of activity in the eye first involved speaks for the presence of true sympathetic ophthalmia rather than the bilateral form of endophthalmitis phacoanaphylactica

Allergy to fish lens protein Because the human lens is tissue specific rather than species specific, hypersensitivity in humans may be induced by lens protein of other animals The danger inherent in such a situation was highlighted when attempts were made to treat cataracts by injections with fish lens protein Posner (110) was the first to point out this danger He reported the occurrence of severe uveitis in one eye of a patient who had received about fifty injections of fish lens extract for bilateral cataracts Intracapsular cataract extraction resulted in cure of the uveitis which had been resistant heretofore In view of the generalized sensitivity to lens protein that was present as a result of the injections it may be postulated that the uveitis occurred due to seepage of lens antigen through a permeable lens capsule Later a milder reaction appeared in the other eye and subsided following cataract extraction

This phenomenon has been further documented by Bremm (111) who reported on three patients with cataracts who had been given injections of fish lens protein Prior to operation two of these developed severe uveitis which he attributed to hypersensitivity In the first patient intracapsular cataract operations performed at the height of the inflammation resulted in rapid quieting of both eyes The third patient manifested severe end

ophthalmitis phacoanaphylactica when *extracapsular* cataract extraction was performed This was the result of previous sensitization to fish lens protein since no previous cataract surgery had been performed

THE SYNDROME OF GLAUCOMATOCYCLITIC CRISES

The syndrome of glaucomatocyclitic crises was first described by Posner and Schlossman (112) in 1948 This entity constitutes one of the few homogeneous groups in the variety of glaucomas associated with uveitis It is a syndrome of recurrent acute noncongestive glaucoma usually associated with mild cyclitis which follows a predictable episodic course The major characteristics which delineate it from the usual secondary glaucomas have been noted by several authors (113)

The involvement is almost always unilateral the pupil of the affected eye is larger than its fellow, and the rise in tension is out of proportion to the symptomatology and the relatively uninflamed appearance of the eye Evidence of cyclitis is minimal consisting of a few cells in the aqueous and an occasional keratic precipitate The angle of the anterior chamber is open even at the height of the attack Recurrences in the same eye are the rule The course is characteristic with the elevation of tension lasting for as long as two weeks but always returning to normal The keratic precipitates may last for a month or longer Between attacks the eye is normal with unimpaired vision and visual fields Provocative tests for glaucoma are normal

Most important in the management of this condition is its recognition and the knowledge that it follows a benign course Surgery is contraindicated as attacks have been known to occur following iridectomy and filtering procedures The control of the hypertensive episode should consist in the use of mild miotics Corticosteroids are very effective and Diamox is helpful if the ocular tension is high No treatment is required between attacks, since miotics will not prevent recurrences

The unusual features of this syndrome, its benign episodic course and its occurrence in certain instances in persons with associated allergies (as noted by Theodore (114)) are the basis for the concept that the disease may have certain allergic features

TREATMENT OF UVEITIS

The vexations and disappointments associated with the treatment of uveitis in the past have in large measure been replaced with a certain optimism since the advent of the steroids which check the inflammatory reaction and the discovery of chemotherapeutic agents capable of eradicating the underlying disease process in certain instances

The three cardinal principles of present day management of uveitis con-

sist in 1) resting the eye with mydriatics 2) curbing the inflammatory process with local and systemic steroids and fever therapy and 3) eliminating if possible the causal agent of the disease

The first of these putting the eye at rest is the time honored method of combating any ocular inflammation through the judicious use of a wide variety of mydriatics heat and dark glasses This therapeusis is sufficiently well known that it requires no amplification here The following discussion will be concerned with the second and third aspects of treatment

Steroid Therapy

Prior to the discovery of the steroids the efforts of ophthalmologists to curb the inflammatory ravages of individual and successive attacks of uveitis were limited to the use of nonspecific protein therapy It was employed on an empiric basis and the results obtained were extremely variable and unpredictable Furthermore the patient frequently required hospitalization and in many instances the age of the patient or associated pathology contraindicated the use of foreign protein therapy With the introduction of steroids and their application to ophthalmology an era was envisaged in which all inflammation could be simply and safely controlled by these hormones The possibility of treating patients on an out patient basis and the relatively few contraindications to the use of steroids opened new and radiant vistas of success in curbing all ocular disease The primary enthusiasm for using steroids in uveitis has now been tested by time and experience it has become evident that while the steroids can curb the inflammatory process they cannot in any way alter the basic pathology responsible for the disease and that in certain instances they are contraindicated It is now realized that steroid hormonal therapy can in itself effect no cures The dramatic and sometimes strikingly successful results in the treatment of uveitis that may occur are due to blocking of the often deleterious inflammatory reaction until the host s natural defenses can gain ascendency and effect a cure

It has been experimentally demonstrated that the beneficial effects of steroid therapy are due to its ability to mask or eliminate the tissue reaction of hypersensitivity and to curb or eliminate ordinary inflammatory reactions secondary to bacterial invasion or to physical irritants

In eliminating the clinical manifestations of the delayed (or bacterial) type of hypersensitivity there is no actual interference with the antigen antibody reaction The effect rather is mediated through the blocking action of the hormones at the cellular level and the inhibition of the inflammatory reaction This action is quite independent of the general physiologic effects of these agents

In curbing the inflammatory reaction due to irritants and bacteria the

effect of the hormones is on the whole deleterious For in suppressing this inflammatory reaction, a simultaneous inhibition of the elementary defense mechanisms of the body occurs Thus phagocytosis is reduced or eliminated fibrosis for bridging areas of destruction is curbed and neovascularization which sustains and nourishes the tissues is inhibited

Initially these noxious effects will not be apparent since the well-being of the patient as a result of the hormones masks the underlying process Thus Woods and Wood (115) and Baum and Drobeck (116) have shown that while under steroids the nonimmune tuberculin hypersensitive rabbit would initially do well while on hormones but when the therapy was discontinued there was an immediate and catastrophic rebound phenomenon resulting in a soft, caseating tuberculous lesion which the host was unable to contain The reparative effects of fibrosis proliferation and phagocytosis not being present the disease ran a rampant course It therefore behooves [illegible] ously with

[illegible] local and systemic administration of the steroids is in the nongranulomatous (or anterior) forms of uveitis The damage which results to the eye in this process is due to a hypersensitive reaction in the sensitized ocular tissues The inflammatory reaction which creates the pathology is due only to the antigen antibody reaction and there is no bacterial invasion or physical irritant involved so that in this instance the steroids with their anti phlogistic effect are ideally suited The inflammation is suppressed until the hypersensitivity has subsided and the reactivity of the tissues has returned to normal If the damage created by the inflammation can be blocked until the allergic episode runs its course the eye will have been protected

In the majority of patients local administration of steroids (in drop form or as ointments) and mydriatics is sufficient to control the irritability of the eye Subconjunctival administration offers no advantage over drops except that it does not require as frequent instillation In patients whose disease is so severe or so protracted that it fails to respond to this regimen systemic administration is effective in halting the immediate reaction Prednisone and prednisolone are steroids of choice because of their ease of administration A customary dose is 10 mg. q i d for a week The dose is gradually decreased depending upon the clinical course of the disease A prolonged low maintenance schedule is often necessary

In instances where the disease remains refractory to the systemic administration of prednisone corticotropin (in gel form for intramuscular administration or in solution for intravenous use) is efficacious in inducing remissions High initial levels of ACTH are administered and the further

dosage schedule is titrated against the clinical response of the patient's disease. The success of corticotropin where corticosteroids have failed implies a stimulation of as yet unidentified fractions of adrenal cortex which are more effective than the cortisone analogues now available.

The rare danger of activating latent herpes simplex infections of the *cornea with use of corticosteroids either systemically or locally must be* borne in mind.

Granulomatous uveitis. Although it is safe to administer systemic steroids with relative impunity to patients with the nongranulomatous variety of uveitis, the opposite obtains in those patients who are afflicted with those types of granulomatous (or posterior) uveitis due to organism invasion. Because of their different pathogeneses, an accurate differential diagnosis between the granulomatous and the nongranulomatous forms of the disease *is essential before placing a patient on systemic steroid therapy.* The local therapy is the same in both diseases.

It is commonly believed that granulomatous uveitis results from an actual invasion of the choroid by organisms—either bacteria, viruses or protozoa—and that the granulomatous reaction elicited is a protective mechanism of the host which walls off the invader from the surrounding normal tissues. As noted previously, where infection is present the steroids with their antifibrotic and anti-inflammatory effects deprive the eye of its normal defense mechanisms and allow the invader to multiply and spread uninhibited. However, while most granulomatous uveitis is due to actual organismal infiltration, the course that the disease takes in the host may be considerably *modified by the hypersensitive state of the ocular tissues. As is well known* the infective qualities of the disease are frequently so modified by the immune or allergic state of the eye that its original characteristics become submerged. The commonest example is tuberculosis. The cultivation of the toxoplasma organism is considerably enhanced in the experimental animal if it is given systemic cortisone, yet it is believed that in the adult human the chorioretinal manifestations of the disease are primarily allergic in nature, which perhaps accounts for the poor response to Daraprim in so many instances.

Therefore, while the systemic administration of the steroids in the infectious granulomatous forms of uveitis is frequently hazardous, they are indicated *when the inflammatory manifestations* result largely from allergy. Unfortunately, the clinical differentiation of these two components is often difficult. Moreover, these difficulties are further aggravated when the original diagnosis is merely a presumptive one.

The principal indications for systemic steroid therapy in *infectious* granulomatous uveitis appear to be involvement of the macular area in the inflammatory process and a high degree of hypersensitivity. *Where the*

inflammatory process threatens the macular area the inflammation must be curbed at a calculated risk The inflammation may thus be controlled long enough to allow the etiologic agent to be diagnosed and treated specifically Where allergy plays a dominant role one is also justified in resorting to the use of systemic steroids despite the danger of further propagating the infecting agent The aim in this instance is to minimize the inflammatory reaction of hypersensitivity and thus protect the delicate ocular structures It is best in these patients to combine the administration of the steroids with a specific chemotherapeutic agent to control the infective character of the infecting agent responsible for the disease

Sympathetic ophthalmia Steroid therapy has considerably improved the once bleak prognosis of this apparently noninfective granulomatous uveitis In the experience of many ophthalmologists fulminating sympathetic inflammation has been arrested and at times apparently cured It is often necessary to administer high dosages for long periods of time perhaps years even though undesirable systemic manifestations of these hormones occur It appears that if the inflammation is suppressed for a long period the disease will ultimately burn itself out The favorable outcome with steroids is another indication of the allergic causation of the disease

It is our feeling however that prophylactic steroids should not be routinely used following perforating injuries of the eye especially during the first two weeks An opportunity to observe the natural unmasked reaction to injury and assess its likelihood of uneventful healing with useful vision is afforded by this fourteen day period of grace during which time the decision to enucleate may usually be safely postponed Treatment with steroids may mask unsatisfactory progress of healing and resolution of the inflammation which would make mandatory prophylactic removal of an unsafe eye We ourselves have encountered an instance where the use of cortisone w

security L

sympatheti

the most intensive steroid therapy McLean (117) has also had a similar experience and long has felt on theoretical grounds that steroids should not be used after perforating injuries

Phacoanaphylactic uveitis The immediate treatment of endophthalmitis phacoanaphylactica consists in the use of steroid therapy both locally and systemically—including if necessary corticotropin in adequate dosage If feasible and otherwise justifiable lens extraction should be performed by the intracapsular procedure Desensitization with lens antigen has been discussed above

Uveitis associated with sarcoid The efficacy of corticosteroid therapy in both the ocular and the systemic manifestations of this disease is now recognized although there are patients who remain refractory to the steroids despite adequate treatment In this disease it is necessary to continue the administration of steroids for long periods until natural remissions occur Recurrences require reinstitution of treatment

Fever Therapy

In the past ophthalmologists were often criticized by their medical confreres for employing nonspecific foreign protein therapy such as boiled milk and *typhoid* vaccine in the treatment of ocular inflammation Yet every ophthalmologist was cognizant of the clinical improvement which followed the judicious use of these agents In recent years it has become evident that the *beneficial effect of this therapeusis has an acceptable* physiological basis in that it induces a demonstrable increase in circulating steroids associated with the elevation of temperature (118)

The wide use of steroids in the therapy of uveitis has tended to entirely supplant the use of fever therapy in the treatment of this disease since most types of uveitis are benefited by steroid therapy However there are occasional instances of uveitis that show no improvement on systemic steroid administration but are improved after fever therapy There is no doubt in our minds that most of the beneficial results obtained from nonspecific protein therapy are engendered by the stress reaction induced by *the high pyrexia Nonetheless it would appear that other factors as* well contribute to the salutary effects of fever therapeusis The superiority of corticotropin over the other corticosteroids is believed to be due to the production of some as yet unisolated fraction of the adrenal cortex It may be postulated that the rare response to fever therapy when the steroids have proven ineffective is due to the liberation of some similar fraction The effectiveness of fever therapy is also enhanced by capillary dilatation increased permeability of the cells and greater blood flow to the diseased tissues All of these factors permit the concentration and penetration into these structures of a greater quantity of antibodies humoral factors and possibly other beneficial substances

Specific Therapy

[illegible]

But this at best is a symptomatic and empiric [illegible] limit the destruction caused by the disease it does nothing to eliminate the cause There is no guarantee against future recurrences While steroids *do much to protect the eye* they may not prevent permanent changes

Each attack causes further damage and may lead to serious functional impairment. It is thus necessary to either eliminate or neutralize the basic cause of the uveitis. The first of these methods consists of the now time honored search for and elimination of foci of infection which may be the source of antigen formation. To a large extent this is unrewarding in our experience. It could well be that many of the definitely diseased structures which are eliminated do not harbor the particular strain of bacteria to which the ocular tissues are sensitive. This may explain the frequent failures. Yet there are many examples of striking cures following the removal of remote infected organs. We all have encountered this frequently enough to justify such an approach. While antigenic foci are usually circumscribed small areas such as the teeth, tonsils or sinuses, this does not always apply. In one patient with recurrent iridocyclitis associated with exacerbations of ulcerative colitis whom we observed, twenty four hours following total colectomy her severely inflamed eye was almost well. The iritis soon subsided and has not recurred in four years.

While there is no question but that the stress of the surgical procedure results in a temporary increase in the concentration of corticosteroids in the blood, we do not feel that this can explain such dramatic permanent results. We believe that beneficial results occur from the elimination of the antigenic focus. This is further borne out by the generally accepted observation that the removal of a responsible focus sometimes aggravates ocular inflammation before improvement takes place. This is explained by probable release of large amounts of antigenic material as a result of surgical manipulation.

Desensitization. Where elimination is neither feasible nor successful, attempted neutralization of the causative process by means of desensitization must be considered. This is usually accomplished by means of either stock or autogenous vaccines, the latter are obtained from cultures of what appear to be diseased structures.

On the thesis that most instances of nongranulomatous uveitis are due to streptococcal allergy, Woods (63) advocates the use of specific stock vaccines based upon reactions to preliminary skin testing. While the validity of this concept has not yet been satisfactorily proven, there are strong indications that the streptococcus plays a primary etiologic role.

The results from the use of such streptococcal vaccines as reported by Woods (63) have been beneficial. Unfortunately, the preparation of the very many different vaccine strains is an extremely difficult and time-consuming procedure which has not been generally adopted, so that relatively few ophthalmologists have had any experience with this method.

Granulomatous uveitis. Advances in chemotherapy have now made it possible to eliminate the specific etiologic agent in several forms of granulomatous uveitis due to direct organismal invasion.

Tuberculosis The direct attack on the tubercle bacillus consists in the administration of isoniazid in divided doses to equal 300 mg daily, for a total of three weeks, to be followed for another three weeks with divided doses totalling 150 mg a day Para-aminosalicylic acid is given in doses of 3 gm q i d One gram of dihydrostreptomycin is given three times a week Therapy is maintained for six weeks In some instances where there is reasonable certainty that the disease is caused by tuberculosis, but fails to respond to the above regime, it may be assumed that hypersensitivity, rather than infection, dominates the picture The treatment of choice here is steroid therapy systemically administered, with the simultaneous use of antituberculous drugs

Desensitization with tuberculin, while theoretically of value, does not appear to be especially effective It is not without danger and treatment must be maintained for long periods of time It is no longer used routinely in the treatment of tuberculosis of the eye

Brucellosis If this rare diagnosis is made, the antibiotic of choice in the treatment of brucellosis is tetracycline Initially it should be administered every four hours in 500 mg doses After four days this should be reduced to 500 mg four times a day This schedule should be maintained for three to four weeks It is no longer felt that adjuvant therapy with sulfadiazine or streptomycin is indicated

Toxoplasmosis At present, treatment of this disease is as follows Daraprim (pyrimethamine) 25 mg once a day, and sulfadiazine four to six gm in daily divided doses for a period of two to three weeks The dose of Daraprim is then reduced to 100 mg a week for another three week period Extreme caution must be employed when using this drug because of its great tendency to cause leukopenia and thrombocytopenia In addition steroids may be used if allergy appears to play a significant role as it frequently does

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ALLERGY AND THE LENS

The crystalline lens is composed *of proteins of complex structure* which have well known antigenic properties Utilizing special immunochemical analyses of extracts of bovine lens, at least eight different antigens have been isolated (1) Phacoanaphylactic uveitis is the resultant allergic reaction which is caused by the effect of these antigens on uveal tissue (chap 19) Whether the lens itself, which is an isolated island surrounded by aqueous, can be the seat of an actual allergic reaction is a question which has not as yet been answered François (2) has demonstrated that congenital cataracts in rabbits may be due to an immunologic phenomenon He maintained that the injection of emulsions of lens tissue into pregnant rabbits caused specific precipitins to pass into the blood of the fetuses Reaction between these maternal precipitins and the lens protein gave rise to small localized opacities which were visible biomicroscopically This would be equivalent to an *allergic reaction While this explanation may*

... cannot

conditions prevail in the fetal lens that are different from those in the adult However, it is possible that under certain situations the lens capsule

... ed by lenticular opaci- with allergic phenomena

It is interesting to note that it has been suggested that the lens may participate in a general allergic reaction. Blankstein (3) reported the history of a patient, age thirty four, who suddenly developed 1.5 diopters of myopia after he had taken 2.5 gm. of systemic sulfonamides daily for 14 days. Accommodation was normal. The following day he developed an allergic dermatitis. Within forty eight hours the refraction returned to normal. This author suggested that the myopia was the result of changes in either the lens or the ciliary body, possibly due to osmotic disturbances secondary to an allergic reaction.

Another instance of transitory myopia, this time associated with an increase in ocular tension, was observed by Schaehne (4). His patient was a thirty nine year old woman who had sudden loss of vision. Four days after the onset of symptoms she had 5 diopters of myopia. On the second day her anterior chambers were moderately shallow, and ocular tension after pupillary dilatation was 30 mm. with the Schiotz tonometer. Under intensive miotic therapy her ocular tension was reduced to 14 mm. At this point Pyribenzamine was prescribed; three days later her refraction returned to emmetropia and her uncorrected vision was again 20/20. The anterior chambers were definitely wider than on the previous examinations and the ocular tension was now 16 mm. even without miotics. This patient had suffered from an episode of angioneurotic edema one year previously following the ingestion of fish. Schaehne attributed the present episode to the fact that the patient had taken quinidine for two weeks prior to its onset. He believed that either the lens had swollen, due to imbibition of fluid, or that perhaps the lens iris diaphragm had moved forward, causing both an index myopia and an increase in ocular tension. The etiologic factor in his opinion was probably either a toxic or allergic reaction to quinidine.

A case with certain similarities to that described above was reported by Barkan (5). His patient had recurrent angioneurotic edema for seven years. Coincidental with these attacks there were symptoms of congestive glaucoma which developed one year after the onset of the edema. On many occasions the ocular tension rose to 35 or 40 mm. of mercury a half hour after swelling of the lower lip, cheeks and tongue. With routine miotics the tension remained normal during subsequent episodes of angioedema. The patient became a Christian Scientist and did not have any further attacks of either angioneurotic edema or glaucoma following her conversion. It is our belief that this patient suffered from attacks of narrow angle glaucoma with each episode of angioneurotic edema.

Posner (6) has speculated that perhaps edema of the ciliary body associated with angioneurotic edema may alone be enough to cause closure of the chamber angle in a patient who has narrow angles. The case de

scribed by Jampolsky and Flom (7) may lend some support to this hypothesis Their patient suddenly developed 5 75 diopters of myopia in the right eye and 4 75 diopters of myopia in the left eye with the onset of menstruation The anterior chambers were extremely shallow but the ocular tension remained normal Ten days later the uncorrected vision and the anterior chamber depth were both normal once more The authors felt that the outstanding feature in this case was the anterior displacement of the lens and that sixty per cent of the myopia could be accounted for on this basis alone Although the etiologic factor in this instance was not established it is probable that this patient did not develop a rise in ocular tension because her chamber angles were basically wide enough and therefore remained functionally open despite the considerable narrowing of the anterior chamber during attack As suggested by Posner swelling of the ciliary body relaxes the zonule by shortening its ring of attachment the lens may now move forward In an already shallow anterior chamber this may cause a rise in tension

These rare reports in the literature give some idea of how the lens may become involved during or coincident with an allergic reaction However by far the most common involvement of the crystalline lens in allergy is the cataract associated with atopic dermatitis

ATOPIC DERMATITIS

There are a number of forms of skin disease which are associated with cataract formation Of such cataracts by far the most important and most interesting as to both pathogenesis and management is the cataract complicating atopic dermatitis

The nomenclature relating to dermatitis due to hypersensitivity has been somewhat confused in the past However with the clarification of allergic concepts in general and of skin reactions in allergy it is now possible to correlate certain apparently unrelated forms of eczema occurring in infants in children and in adults The evolution of this approach has been summarized by Hill and Sulzberger (8)

Infantile eczema is the dermatitis in infants due to hypersensitivity to protein substances This is an acute vesicular dermatitis and differs in appearance from the chronic dermatologic condition observed in *children* and adults known as neurodermatitis However Hill and Sulzberger stress the fact that the fundamental basis *of atopic dermatitis is the same at all* ages even though its clinical appearance in infants is *markedly different* from that of the neurodermatitis of later life More recently Hill (9) reaffirmed this belief and stated that atopic dermatitis is a constitutional disease like diabetes and pernicious anemia The patients have the same constitution that underlies hay fever and asthma As with asthma there

is an abnormal immunology—but other stimuli, especially psychogenic, affect it

As long as it is realized that atopic dermatitis is the same disease in both infant and adult, modified by the different terrain and repeated dermatologic insults the actual nomenclature is relatively unimportant For clarity, however, the terms chronic atopic dermatitis or chronic atopic eczema would appear preferable to neurodermatitis An objection to this use of the word atopic could be raised on the basis of the fact that an actual antigen-antibody cause is not demonstrable in many cases although it is generally accepted that a majority of the individuals so affected are atopic Hampton and Cooke (10), Simon (11, 12) and others have reported that a large proportion of patients with atopic dermatitis show immediate urticarial reactions to intradermal skin tests with extract of human epithelium These observations suggest the possibility of autosensitization to antigens of the skin

Atopic dermatitis occurs in an individual who has a hereditary predisposition to atopy However there is a predisposing condition in the skin which is not present in those individuals who have hay fever or other atopies alone Hill (9) calls this the "x-factor" This difference in reaction between the average atopic patient and the one who has atopic dermatitis is manifested by the fact that if the atopic patient for instance is given too much ragweed extract by inoculation he will develop an urticaria in atopic dermatitis there is a very low tolerance to ragweed and this patient if given any more than the smallest dose will experience a worsening of his eczema or the development of a new skin eruption The dose needed to produce this reaction is much less than that necessary to produce an urticarial reaction in the average atopic individual

There are three stages of the disease

First stage The three month-old infant develops a papulovesicular rash on the cheeks It then extends to other areas of the body, especially the legs forearms breast and forehead There may be little or no oozing and just irregular areas of erythema, however, the most characteristic lesion is an exudative papule The eruption may become generalized

It is believed that the capacity for sensitivities starts in embryonic life and may run from infancy to middle age The atopic individual goes through life constantly acquiring new hypersensitivities as he becomes exposed to new allergens, and losing some of those allergies which he manifested earlier in life In infancy, sensitivity to eggwhite is most common, but milk, wheat, house dust, pollen, wool, silk and cat dander are important allergens

Second stage This extends from two to twelve years of age The characteristic cutaneous lesion is papulation and the common sites are the ante

cubital and popliteal spaces, the wrists and the region around the neck. The skin becomes thickened, erythematous and hyperpigmented. The picture is varied, however; if vesiculation occurs it is only secondary. Pruritus is very intense.

Third stage. In a large percentage of cases the dermatitis disappears during infancy or childhood and does not recur. However, in some individuals atopic dermatitis persists during adult life. A large percentage of these patients have a familial history of other atopic manifestations such as asthma and hay fever or themselves have a personal history of atopic disease. There is, nevertheless, a small group in which atopy cannot be proven. The adult form of atopic dermatitis is similar to that of childhood. The antecubital and popliteal fossas, the forehead, region around eyes and the back and sides of the neck are common sites. There are slightly elevated papules and diffuse, dry, slightly scaly, hard and thickened, usually not very sharply demarcated lichenified plaques with accentuation of the cross markings of the skin. Some of the papules become excoriated. There is oozing, weeping and crusting. There are often superimposed impetigenous or mycotic lesions. There is constant pruritus. The disease is chronic and there may be fairly long intervals in which the patient is free from symptoms. Sometimes the entire skin of the patient finally becomes grayish brown and on the face, neck and antecubital areas the hue may be so characteristic as to suggest the diagnosis at first glance.

The hypersensitivity of the skin of patients with atopic dermatitis is most extreme. They exhibit multiple allergies of the immediate variety to intracutaneous and scratch tests. However, these positive reactions are not necessarily the direct cause of the skin lesions, except in the first two years of life. They merely indicate the allergic propensities of the patient. Blood eosinophilia is usually slightly elevated.

ATOPIC CATARACT

The cataractous changes that occur in atopic dermatitis are essentially of two types: 1) the classical cataract of atopic dermatitis and 2) the more common so-called complicated cataract. Beetham (13) has emphasized these two varieties and found in ten patients that ten out of eighteen cataracts belonged to the second group. However, others have observed the complicated variety to occur even more frequently. In our experience the disease is essentially bilateral although occasionally considerable periods of time may lapse before development of the second cataract. While a few American authors (13–15) have noted unilateral occurrence, Sack (16) in an extensive survey of all cases reported up to 1947 found that of thirty American cases only eight were unilateral and that all twenty-eight of the European and Australian cases were bilateral.



FIG 110 Cataract in atopic dermatitis (*Left*) Anterior cortex (*Right*) Posterior cortex (Bellows J G *Cataract and Anomalies of the Lens* C V Mosby 1944)

Classical cataract of atopic dermatitis This form was originally described by Vogt (17) as the cataract of neurodermatitis Here a dense irregular plaque of opacity usually white or gray forms in the anterior or posterior cortex (fig 110) It involves to some extent the pupillary area immediately beneath the capsule The capsule overlying the opacity can become wrinkled and elevated In the course of time the entire lens becomes opaque

Complicated cataract In contradistinction to the first variety this type of opacity begins at the posterior pole just beneath the capsule There is increased iridescence with vacuole and precipitate formation Striations of the cortical fibers develop simultaneously Later the changes spread more peripherally to involve the entire posterior subcapsular area Small punctate opacities are frequent Still later similar changes take place in the anterior subcapsular area These processes gradually progress and the entire cortex becomes cloudy forming an intumescent or else a homogeneous mature cataract We find it difficult to differentiate such cataracts from other types of complicated cataracts or from cataracts occurring in retinitis pigmentosa various endocrine dyscrasias neurogenic disturbances and other skin disorders

Incidence of Cataract in Atopic Dermatitis

Little attention has been paid to the actual incidence of cataract in atopic dermatitis One hundred consecutive patients with this disease were examined by Cowan and Klauder (18) for the presence of noncongenital lenticular opacities as compared to a control group of persons with no

skin abnormalities In one hundred normal patients lenticular opacities were *found in twenty eight per cent* Opacities were bilateral in twenty patients In the patients with atopic dermatitis twenty six per cent of all patients examined had lenticular opacities These statistics show that lenticular opacities revealed by biomicro copic examination are no more common among patients afflicted with atopic dermatitis than they are in a control group However in the nonatopic group there was not one grossly demonstrable cataract or a potentially progressive one On the other hand in the atopic group eight patients showed some stage of development of cataracta complicata This incidence of eight per cent agrees with the findings of Brunsting who reported ten per cent

Cowan and Klauder s cases of atopic cataract seem to fall into the two *categories described above In several instances overlapping with char*acteristics of both types is described

The cataract associated with atopic dermatitis generally occurs in the third decade of life The average age as reported by Cowan and Klauder was 23 3 years the youngest was eighteen years In one of Beetham s cases the cataract began in infancy in the others of his series with one exception the cataract started before thirty years of age Forty six years was the oldest reported age of onset (19) until 1946 when Cordes and Cordero Moreno (20) published their observations in four cases including a patient who first developed atopic cataract at the age of forty nine

Pathogenesis of Atopic Cataract

The pathogenesis of atopic cataract is still obscure A number of theories have been advanced but all of them are open to various objections There *is no question however* that cataract occurs relatively frequently in patients with atopic dermatitis

While skin manifestations must occur at some time during the course *of the disease in patients with atopic cataracts they need not* be present at the time when cataracts begin to develop In fact the first appearance of the dermatitis may precede the lenticular opacities by many years and in some cases may have *completely disappeared long before the eyes are*

a rapidity independent of the severity or even the actual presence of the dermatitis

Studies in the causation of atopic cataract reflect the *different trends* in thinking at various stages in the development of modern medicine Among the many suggestions put forward the following four concept appear to merit consideration 1) vitamin and amino acid *deficiencies* 2)

endocrine and metabolic disturbances 3) dysfunction of the autonomic nervous system in conjunction with psychogenic factors and 4) atopy and other allergies At the present time it seems to us that allergy would appear to play a dominant pathogenic role

Vitamin and amino acid deficiency Both cataracts and dermatitis have been produced in rats on diets deficient in certain amino acids Such cataracts have been observed in young rats never in adults In general these cataracts have certain morphologic similarities to the atopic cataract of humans Tryptophan and riboflavin deficiency results in cataract dermatitis and alopecia A similar type of lenticular opacity is associated with thallium poisoning Buetti s (21) work indicated that the latter is probably related to vitamin deficiency because it can be prevented by feeding rats with brewers yeast and, to a lesser extent, with liver extract It appears to us that while such experimental cataracts may simulate to some degree the opacities occurring in atopic dermatitis they fail to explain the basis for atopic cataracts There is no evidence either clinical or experimental that vitamin deficiency is etiologically important in such cataract formation

Endocrine and metabolic disturbances Cataracts have been reported resulting from deficiencies of the pancreas thyroid and parathyroids These are in many ways similar to atopic cataracts and usually occur in young individuals

Among those cataracts produced by disturbances in carbohydrate metabolism are the true diabetic cataracts occurring in man and the experimental cataracts in pancreatectomized dogs and rats Cataracts have also been produced in rats (22) rabbits and mice (23) by feeding these animals on diets high in lactose galactose or xylose (24) Galactose cataracts have been observed in children

Cataracts may occur in hypoparathyroidism either in the idiopathic form or following operative removal (25 26) Similar lenticular opacities have been produced experimentally in dogs (27) rats and rabbits (28)

Although there are many references to the association of cataract with myxedema and five cases are reported in the literature the relationship is not clear cut Buschke (29) made the observation that in view of the relative frequency of myxedema and cretinism one would expect cataract to occur more frequently in either of these conditions if thyroid deficiency were a primary factor in the development of cataract

Lowenstein (30) felt that the cataract in atopic (neurodermatitis) dermatitis belongs to the group of cataracts due to disturbances in the mechanism of inner secretion This belief is based on the similarities in the clinical appearance of hormonal and atopic cataracts Buschke (29) felt that there is a primary hereditary metabolic disturbance in the tissues of

the affected organs in the entire dystrophic group of cataracts (atopic cataracts are one form of this type) He believed that this primary metabolic disturbance rather than a primary endocrine dysfunction is responsible for cataract formation However, there is little or no evidence relating endocrine and metabolic aberrations to the causation of atopic cataracts The basal metabolic rate as well as blood calcium and phosphorus concentrations are normal in patients with atopic dermatitis, both with and without cataracts This would appear to exonerate the thyroid and parathyroids The incidence of diabetes or other endocrine disorders is very low in atopic dermatitis

Autonomic dysfunction and psychogenic factors. Originally the term *diffuse neurodermatitis* was used to emphasize the relationship of this dermatologic condition to a disorder of the sympathetic nervous system It has also been suggested that an autonomic instability furnishes a suitable terrain for the allergic disturbance Many patients give a history of an exacerbation of symptoms following emotional upsets Beetham makes the observation, however, that in a fourteen-week-old infant it is impossible that the nervous system could be so irritable and hypersensitive as to cause cataracts As in many other allergies especially those of cosmetic nature, emotional effects often occur secondarily and may by their intensity be given greater significance, etiologically, than they deserve

Vidal (31) was the first to call attention to the role of the psyche in atopic dermatitis, he described such patients as being nervous, anxious and unstable Hill and Sulzberger believed that the emotional background was so important that they advocated putting the patient into a "controlled environment" in order to eliminate emotional problems McDannald (32) called attention to "emotional immaturity" in two cases of atopic cataract Cordes and Cordero-Moreno as well as Milner (33), were also impressed

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[illegible] dermatitis, it is difficult to understand how they could possibly act as a primary etiologic mechanism in the formation of the cataract itself In this connection Hill (9) recently stated that the psychiatric aspects of atopic dermatitis have been overemphasized

Atopy and other allergies. The role of allergy as the major etiologic [illegible] fact The allergies these pa

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irritants

The basis for an allergic etiology for atopic dermatitis is summarized as follows 1) Hereditary background of atopic allergies in other members of the same family, who may have asthma, hay fever and various skin

sensitivities is present in the great majority of patients 2) There is a personal history of all types of allergic manifestation especially of the atopic variety Asthma hay fever urticaria migraine gastrointestinal disturbances vasomotor rhinitis all occur 3) Fifty per cent of patients demonstrate blood eosinophilia 4) The results of intracutaneous skin tests in one hundred patients were reported by Brunsting (14) Using many antigens including ragweed orris root wool silk house dust animal emanations hair and foods he obtained positive reactions in seventy of the patients so tested Positive reactions were distributed in the various groups as follows ragweed 32 orris 25 silk wool and house dust 21 animal dander and other emanations 29 foods 40 Such skin tests in atopic dermatitis are not necessarily conclusive because the allergen which gives a positive skin test is not necessarily the one which causes the skin eruption

It must be remembered however that as in vernal conjunctivitis whose terrain is somewhat similar to that of atopic dermatitis these allergic components especially as the patient grows older and sheds his infantile allergies assume less importance as precipitating factors although they continue to predispose the patient to his ectodermal reaction

In the absence of direct experimental evidence the basis for considering the cataract that complicates atopic dermatitis as allergic lies in the nature of the disease itself In this connection it is interesting to observe that both the major shock organs involved the skin and the lens are ectodermal in origin Other skin lesions such as scleroderma and poikiloderma atrophicans may be associated with lenticular opacities It should also be borne in mind that the cornea likewise of ectodermal origin may sometimes be affected in atopic dermatitis (keratitis and keratoconus) The allergic mechanism responsible for atopic cataract has been considered by several authors

Daniel (15) believed that an alteration in the secretory cells of the ciliary body occurs similar to changes in the skin Thus toxins or allergens are produced which in turn affect the lens permeability and produce opacifications

In discussing Daniel s paper Woods (34) conjectured that the lens may participate in the general cutaneous allergic reaction and thus the permeability of the capsule may be altered If aqueous filters through the altered lens capsule opacification would take place much in the same manner as in a traumatic cataract In order to explain this type of reaction the aqueous would have to contain certain specific allergens Woods suggested that the aqueous of patients with atopic cataracts be used as a skin antigen in these patients Beetham performed such intradermal injections of the patients own aqueous in two cases of atopic cataract but failed to obtain any skin reactions Two negative results are certainly not conclusive so

that one must await further reports before establishing that there are no circulating antigens in the aqueous

Cordes and Cordero Moreno felt that the lens at times may be an atopic shock organ in a manner similar to the skin conjunctiva mucous membrane bronchi or gastrointestinal tract Thus a patient with a history of atopic dermatitis may develop a cataract even though there is no dermatitis present at that time It is difficult for us to understand how the lens can be a shock organ because it is isolated from the blood stream unless the antigen gets into the aqueous through the blood aqueous barrier which as we have just indicated has not been proved

Coles and Laval (35) have called attention to the possibility that the alpha globulin of the lens plays a role in the development of cataract and that the allergenic properties of the alpha fraction are in some way related to the allergenic factors in the skin

It is our feeling that atopic cataract like atopic dermatitis is an allergic manifestation of a relatively complex and not yet elucidated nature occurring in specially predisposed and conditioned atopic individuals somewhat similar to vernal conjunctivitis Thus the allergy does not appear to be a simple one of the classical varieties although such associated allergies are present Other factors such as endogenous or even autogenous allergy operating in allergically predisposed individuals may possibly cause atopic cataract Since the lens is known to have several antigens it

some manner and form an antigen antibody reaction in the lens cau i g opacification This assumes that lens antigens can react to nonspecific antibodies and also that such antibodies actually enter the aqueous and pass through the lens capsule Utilization of passive transfer techniques may offer some evidence for the latter two assumptions The experiments of Beetham where negative reactions occurred when autogenous aqueous was injected intradermally might be explained by the fact that antibodies rather than antigens were injected and could not incite an allergic skin response in the same patient This idea is purely speculative However it is interesting to note that two observers (14 20) have emphasized the special thinness of the lens capsule in atopic cataract This may favor the penetration of antibodies into the lens

Other Dermatoses Associated with Cataract

A certain amount of confusion has arisen because cataract is associated with a number of dermatologic conditions The actual differential diag

TABLE 12

Cataract syndromes with atrophic dermatosis other than atopic cataracts

1 *Rothmund's syndrome*
  a Poikiloderma vasculare atrophicans (a telangiectatic condition of the skin)
  b Atrophy and underdevelopment of the gonads in both sexes
  c Cataract develops early in childhood usually between fourth and sixth years
  d Probable recessive inheritance
2 *Werner's syndrome*
  a Scleroderma with ulceration of skin of lower extremities premature graying of hair and baldness
  b Atrophy of the testicles and aspermatogenesis in the male premature sexual involution in the female
  c Hyperparathyroidism
  d Adenomas of the thyroid and adrenal cortex
  e Changes in the blood sugar
  f Keratitis bullosa
  g Cataract develops in the third or fourth decade of life
3 Cataract associated with keratosis follicularis (Darier's disease) telangiectasis and myxedema
4 Juvenile cataract associated with anomalies of the hair

nosis of atopic dermatitis from other skin lesions lies within the realm of the dermatologist What makes the skin conditions of interest to the ophthalmologist is the cataract that may occur in all of them The first to describe cataract as a complication of a dermatosis was Rothmund (36) who in 1868 observed this occurrence in poikiloderma In 1904 Werner (37) noted lenticular opacities in scleroderma Cataract in the course of the disease which we now recognize as atopic dermatitis was first reported by Andogsky (38) in 1914 and has been referred to as Andogsky's syndrome Table 12 adapted from Buschke (29) lists the salient features of the other conditions

Special Aspects of Atopic Cataract Surgery

Although many authors have implied that cataract extraction in patients with atopic dermatitis offers no greater hazards than those entailed in the surgery of ordinary senile cataract recent experience indicates that serious complications are by no means rare Thus, surgery must be planned to minimize these sequelae as much as possible

The complications are the usual ones that are encountered in cataract surgery in general However several of these particularly retinal detachment, but also iridocyclitis secondary glaucoma retinal edema and hemorrhage, all appear to occur in greater incidence in atopic cataracts than in the usual senile cataract Vogt (17) emphasized the severe iridocyclitis and Metzger (39) the frequency of retinal bleeding The valuable study of

Coles and Laval (35) pointing out the special tendency of patients with atopic cataract to develop retinal detachment preoperatively as well as postoperatively has placed the importance of the whole subject in proper perspective From a survey of the literature they ascertained that of twenty one eyes reported as blind or enucleated retinal detachment was present in twelve To this high incidence they added two eyes from the case they described making a total of fourteen eyes It is difficult to establish the exact percentage incidence of this complication Moreover many reports in the literature give incomplete data and the follow up is not sufficiently long Furthermore detachment existed preoperatively in some cases However in a broad sense there is an apparently great tendency for patients with atopic cataract to develop retinal detachment

The cause of the detachment of the retina that occurs is not known Not only may detachments exist before surgery for atopic cataract (20 40) but they have also been observed in the absence of cataract in patients suffering from atopic dermatitis (41) This suggests that a mechanism somewhat similar to that causing the dermatitis may play a role by so altering the vitreous and retina as to predispose the patient to detachment Cataract extraction may act as the precipitating factor in such a predisposed individual

The choice of surgical procedure in atopic cataract requires special consideration to be given to those factors likely to influence the occurrence of the complications discussed above Current statistics show that there is

[illegible]

tempts at dislocation during the extraction may result in vitreous loss potentiating detachment Moreover Cordes and Cordero Moreno and also Brunsting have emphasized that the capsule is especially thin in atopic cataract—which of course increases the tendency for capsular rupture On the other hand if extracapsular extraction is planned it is important to leave as little anterior capsule and cortex behind as possible to avoid thick secondary membrane formation In such cases discission may result in eventual detachment of the retina While iridocyclitis is greater in the extracapsular operation this may be controlled by steroid therapy Sometimes in immature cataracts a preliminary opening of the capsule twelve to twenty four hours before extraction is necessary (Homer Smith) Our own experience with the extracapsular method on the whole has been satisfactory

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21

ALLERGY OF THE RETINA AND OPTIC NERVE

The optic nerve and retina are frequently the site of reactions resulting from exposure to various types of noxious agents. While most of such phenomena are obviously toxic in nature, often definite allergic manifestations appear to occur. Before discussing the latter, it is necessary to distinguish between these two types of reactions.

DIFFERENTIATION BETWEEN ALLERGY AND HYPERREACTIVITY

While everyone accepts the fact that external poisons when taken in toxic doses will result in tissue death, it is generally not realized that in certain hyperreactive individuals minute amounts of the same drug may result in a similar reaction. It is apparent that this is not an allergy, in that the person so affected reacts in a manner only quantitatively different from that of the average person. A great deal of confusion arises in regard to the differentiation of what we call drug hyperreactivity from true drug hypersensitivity or allergy. Most persons will react to large doses of atropine taken internally with the classic pharmacologic and toxic actions of the drug, such as vomiting, tachycardia, fever and dilatation of the pupil. When, however, an individual reacts in the *same manner with the same symptoms* if he ingests a very small amount of atropine or reacts similarly after its local instillation into the eye, this is in a sense a toxic effect following a minute dose. In other words, the only difference in the reaction here is a quantitative one as regards dosage. In drug hypersensitivity, however, the person affected responds with entirely different symptoms, essentially allergic, such as asthma, rhinitis, urticaria, rashes, fixed eruption, and other accepted allergic reactions. These are not pharmacologic effects of the drugs, and when they do occur they are the same no matter what particular drug the patient has used.

Varying terminologies are responsible for difficulties in differentiating

basic types of drug intolerance We prefer the term hyperreactivity for the phenomenon described above in which the individual reacts in an entirely pharmacologic manner to minute doses By hypersensitivity reactions we mean typically allergic responses

Individual variations make it difficult to ascertain exact toxic retinal dosages These often vary with the specific affinity of the agent for neuroretinal tissue as well as the person involved Thus with methyl alcohol the damage is usually proportional to the amount ingested and always will cause serious damage, whereas the exceptional individual who develops blindness from quinine almost always would appear to be a hyperreactive individual He is not allergic, he merely exhibits pharmacologic and toxic manifestations at a dosage level at which most persons do not If this were not so then quinine amblyopia would be far more common considering the extent of its use The rare person who is allergic to quinine does not exhibit such pharmacologic and poisonous effects, instead he shows generalized symptoms of allergic and anaphylactic nature

Hyperreactivity would appear to play an important role in tobacco amblyopia where only the rare overreacting individual of the many millions who do smoke, develops visual difficulties Moreover we have encountered patients who have complained of blurring of vision following a few puffs of a cigarette This is probably due to contraction of the retinal vessels or perhaps of the choroidal vessels which supply the macula Such individuals may also manifest tobacco angina with attacks of anginal pain due to coronary spasm in the absence of organic coronary disease

Other important examples of hyperreactivity that may be encountered by the ophthalmologist are the rare untoward reactions sometimes occurring following the use of atropine and cocaine Some infants are so hyperreactive to atropine that death has occurred after the instillation of one drop of two per cent solution Similar experiences can occur with cocaine While hyperreactivity seems more apt to occur in sympathicomimetic individuals other less dramatic reactions have followed the use of pilocarpine mecholyl carcholin and other acetylcholine analogues Such examples include individuals who develop marked ciliary spasm from as little pilocarpine as one quarter of one per cent accompanied by pain and three to four diopters of myopia

While retinal allergy is not common, nevertheless a number of case reports have appeared in the literature The evaluation of these reports is difficult and at times leaves something to be desired It must be realized that since the proof of the allergic nature of such reactions by specific testing is at best only indirect a great deal of stress is of necessity placed on the history and clinical course of the disease This unfortunately limits the value of many observations

TABLE 13

Neuroretinal allergy

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1 *Anaphylactic and atopic reactions*
  - a Serum
  - b Food
  - c Pollen
  - d Drug
  - e Angioneurotic edema and urticaria

2 *Microbiallergic reactions*
  - a Tuberculin
  - b Other organisms

3 *Other reactions of possible allergic origin*
  - a Eye changes in periarteritis nodosa
  - b Central angiospastic retinopathy

CLASSIFICATION OF NEURORETINAL ALLERGY

In general, allergic reactions of the retina and optic nerve appear to follow the usual lines of allergy elsewhere With the exception of contact allergy which obviously cannot occur anaphylactic atopic and microbiallergic reactions have been noted Following the classification of allergy used elsewhere in this book the retina and optic nerve are subject to the types of allergic reactions as shown in table 13

In contradistinction to toxic and hyperreactive affections of the retina and optic nerve which reveal little immediate objective evidence of tissue involvement so that diagnosis depends on subjective findings especially central vision and visual fields in most instances of neuroretinal allergy the reactions are exudative and hemorrhagic so that they are readily apparent on ophthalmoscopic examination The only major exceptions would appear to be those rare cases of retrobulbar neuritis on an allergic basis

Bettman (1) has described four clinical manifestations of allergic retinosis 1) edema due to sera or food 2) retinal hemorrhages 3) retinal detachment and 4) recurrent neuroretinitis due to pollens He has suggested that retinal hemorrhages may be due to increased capillary permeability They may be superficial or deep and on rare occasions may simulate the picture of closure of a branch of the central retinal vein

In the optic nerve allergic reactions give two types of clinical pictures *1) edema of the nervehead with or without concomitant retinal edema* and 2) retrobulbar neuritis

In this book allergy of the retina and optic nerve will be discussed together because in many cases both tissues are involved simultaneously and on the other hand the same allergen may cause a retinitis in one instance and a neuritis in another

NEURORETINAL ALLERGIES FOLLOWING SERUM SICKNESS

Before the advent of chemotherapy when appropriate antisera were used in the standard treatment for pneumococcus pneumonia or for cerebrospinal meningitis serum sickness occurred as a relatively frequent complication of this form of therapy Since this condition occurred in very sick patients and was treated by internists ophthalmologists were rarely called in consultation Consequently retinitis papillitis and neuroretinitis as part of the picture of serum sickness may well have occurred much more commonly than the few case reports in the literature would have us believe

Mason (2) reported two cases of serum sickness due to pneumococcus antiserum and one due to meningococcus antiserum The first patient was a twenty five year-old man with type I pneumonia He was given 500 cc of antiserum intravenously on the third fourth fifth and sixth days of the disease On the ninth day the patient developed severe serum sickness Although the temperature had been normal, it now rose to 104°F and an urticarial rash developed on the eleventh day At this time both retinas showed edema the disk margins became blurred and a small hemorrhage appeared along the superior branch of the left temporal vein The fundi gradually returned to normal except for slight residual blurring of the disk margins and obliteration of the cups by new connective tissue The second patient developed mild optic neuritis at the height of the serum sickness which was also due to pneumococcus antiserum type I The third case was a child with epidemic cerebrospinal meningitis in whom mild optic neuritis developed without visual disturbances The last two cases were discovered by Mason after he began to look for them routinely in cases of serum sickness

Bedell (3) showed the fundus picture of a patient with edema of the nervehead and retina following injection of tetanus antitoxin The patient developed an urticaria within a few hours after receiving the antitoxin Shortly afterwards the fundus revealed edematous thick white swellings which obscured the nervehead These swellings appeared like irregular balloons of various sizes and prominence The arteries were normal but the veins were at least twice their normal size There were several superficial hemorrhages The swelling rapidly decreased and seven weeks later the disk was almost perfectly round The veins were still fuller than normal On the temporal side of the slightly pale disk there were several yellowish brilliant remnants of former edema and in the vitreous in front of the macula there were many fine gray pinpoint dots (fig 111, bottom right)

Kennedy (4) reported a case of serum sickness following the administration of tetanus antitoxin in a four year old boy He developed aphasia right hemiplegia hemianopia papilledema and edema of the retina This

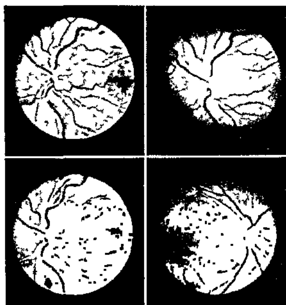


FIG 111 Allergic fundus reactions (*Top left*) Petechial hemorrhages in the retina in patient sensitive to procaine (*Top right*) Same patient resorption (*Bottom left*) Recurrence 2 months later following another injection of procaine (*Bottom right*) Allergic edema of the retina and nerve head due to tetanus antitoxin Although photograph was taken 6 weeks after serum reaction occurred, some edema still was present (Bed ll (3))

much as there was increased intracranial pressure, it is difficult to assess just how large a role allergic neuroretinitis played in the picture Kennedy, however, believed that the meninges were the seat of allergic swellings similar to the retina and skin The same author (5) reported another case of serum sickness in a boy of eleven years following the use of scarlatinal prophylactic serum Four days following the injection of the serum, this child developed a clinical picture similar to the one described in the case above

Bothman (6) reported a case of preretinal hemorrhage occurring in a twenty four-year-old man who developed urticaria and generalized edema twenty-four hours after the injection of tetanus antiserum Vision of the right eye was reduced to finger-counting at five feet There was one diopter of papilledema as well as a hemorrhage in the macular region which lasted for [illegible] eturned to normal

[illegible] with serum sick-

ness in whom the temperature varied from 100 to 101°F with moderate reactions. These cases followed the intravenous injection of 10 000 units of diphtheria antitoxin. Serum sickness occurred on the eighth to the twelfth day following the injections. When second doses were given some months later allergic reactions occurred within twenty-four to forty eight hours in some of the patients. These included fever, arthritic and muscular pains, urticaria and edema. Out of seventy five such cases of serum sickness nine patients complained of blurring and spots before the eyes. Prominent ocular signs were dilatation of the pupils and vasodilation of conjunctival vessels with profuse lacrimation. The retinas showed dilation of arteries and veins and hyperemia around the disk. Some patients developed definite papilledema and the retinas showed "watered silk" appearance. The ocular findings were greatest when urticaria was at its height.

OTHER ATOPIC REACTIONS OF THE RETINA AND OPTIC NERVE

Foods, Pollens and Drugs

Retinal and optic nerve allergy have been reported due to foods, drugs and pollens. One of the most interesting cases of food allergy is that reported by Plummer (8) concerning a physician who was hypersensitive to peanuts. The patient had an allergic diathesis with migraine, hay fever, and an intolerance to chicken. Skin tests showed sensitivity to chicken meat, pollens of early grasses, beans, cottonseed and peanuts. His chief complaint was blurring of the vision. There were congestion and haziness of the left macular area. Recovery took place within a short period of time. Some weeks later the patient had another attack. Since he was a physician and interested in allergy to foods he was able to trace the cause of his condition to peanuts which he had ingested immediately prior to each attack.

Criep (9) examined a case of transient amblyopia and blurred disk which occurred whenever a patient ate fish.

Chocolate has been indicated as the cause of retinal allergy by Bothman (10) and Ruedemann (11). Bothman's case involved a woman who had suffered attacks of migraine after eating chocolate. *On one occasion after* eating several pieces of chocolate candy she had a severe attack with nausea, emesis, blurring of vision and spots before the right eye. Vision was 20/40, the margins of the right disk were blurred and a temporal hemianopia was present. Vision improved to normal in three hours and the disk became normal in three weeks. Ruedemann reported a similar case which occurred after eating *chocolate or nuts*. Galleman's (12) patient was a man with transitory amblyopia, scintillating scotoma and temporal

amblyopia during an attack of migraine Both disk margins were blurred These attacks followed ingestion of milk

Hayden and Cushman (13) observed recurrent bilateral optic neuritis in a patient with extreme hypersensitivity to milk and eggs Visual impairment was correlated with the ingestion of these products In one eye optic atrophy resulted in the other eye however less damage occurred and vision returned to normal When the patient abstained from milk and eggs no recurrences were noted in this eye in the ensuing ten years

Pollen sensitivity may also cause edema of the optic nerve Ruedemann (14) reported a case in which papillitis was due to primrose In another paper Ruedemann (15) cited a case of neuroretinitis which recurred annually during the hay fever season

Allergy to drugs has also been cited as a cause of retinitis and optic neuritis Chief among those reported are sulfanilamide sulfapyridine and procaine Duggan (16) has called attention to a case of bilateral optic neuritis with unilateral sixth nerve paralysis in a boy of seven who received sulfapyridine Bucy (17) described a toxic optic neuritis due to sulfanilamide This case is included by us because we feel that the mechanism may be allergic

Bedell (3) reported a case in which procaine was probably the offending allergen A fifty year old woman consulted him for poor vision in the left eye of eleven days duration The vision in this eye was 20/50 There was edema of the entire retina with many superficial striate as well as deeper hemorrhages The macula appeared as a clearly outlined irregular dark oval surrounded by deep retinal hemorrhages and petechial hemorrhages The inflammation gradually subsided in two months However two months after this improvement had occurred the patient returned with a similar picture following the extraction of a lower molar with procaine anesthesia The patient had an eosinophile count of 15 per cent (fig 111)

Angioneurotic Edema and Urticaria

Generalized reactions falling into this category may involve the optic nerve and retina Bettman (1) observed a highly allergic patient suffering from hay fever allergic rhinitis asthma and allergic keratoconjunctivitis He was sensitive to numerous antigens and had a family history of allergy In the eye that was later to become involved the vision was already reduced to 20/50 because of keratitis believed to be allergic in origin At this time edema of the macula suddenly occurred reducing the vision still further to 20 200 He was seen shortly thereafter and given one cubic centimeter of epinephrine hydrochloride One half hour later the visual acuity returned to 20 50 In the next few hours vision again diminished

but responded favorably once more to the administration of epinephrine in oil The edema gradually subsided within several days The edema was confined to the vicinity of the macula Bettman points out that the tendency of the macula to become edematous is due largely to the thickness of the internuclear layer of the retina and the marked choroidal capillary network in this region

Coca (18) reported a similar case in a patient with a highly allergic personal and family history She had suffered from hives at the age of twelve and was sensitive to lemon cornstarch commercial gelatin strawberries and peaches At seventeen, she had severe symptoms of indigestion and finally was relieved by gastroenterostomy Gastritis headache and abdominal pain occurred regularly She then had two episodes of hematuria and intestinal bleeding Migraine first appeared at twenty seven and increased in severity until middle age During a period of residence in the Philippine Islands she was free from attacks Some time later sudden *blurring of vision of the left eye occurred during the summer* disappearing in the fall Cloudy vision again reappeared the next spring On a boat trip to Panama one week out of New York, vision in the left eye cleared completely and was perfectly normal until ten days after the patient's return to New York

Edema of the optic nerve is occasionally associated with allergic phenomena Kennedy (5) reports a man in his forties who had angioneurotic edema The patient developed attacks of blurred vision of duration varying from a few days to several weeks Kennedy studied the fundus changes at both the beginning and the end of these attacks for hours at a time He could see the obscuration of the disks by what appeared to be puffs of smoke blown across the retina In the course of the illness the man became completely deaf but later regained his hearing

In the discussion of Kennedy's paper Brickner (19) described a highly allergic patient who had had two attacks of blindness with swelling of the disks and frequent signs of great weakness suggesting cataplexy The relation of the neural symptoms to the allergic exposure had not been completely worked out

Handwerck (20) reported the case of a woman aged seventy five who developed what appeared to be giant urticaria and angioneurotic edema During the attack he noted a swelling of the right disk measuring two diopters in elevation Ullmann (21) reported similar papillitis in a man with swelling of the back of the hands pharynx and lacrymal mucosa and focal epilepsy due to angioedema

Bassoe (22) described a patient with increased intracranial pressure headaches choked disk and vomiting without localizing signs A decompression operation was performed Fifteen years later the patient had a

severe attack of angioneurotic edema with swelling af all parts of the body and intermittent edema of the joints, which caused Bassoe to consider a possible allergic basis for the original episode It might be observed that edema of the optic nerve may be a primary manifestation of allergy At other times, the allergic reaction may cause edema of the meninges, or the brain so that choked disk results from the increased intracranial pressure

Albracht (23) also described a case of papillitis associated with angioneurotic edema but here the edema of the disk apparently was not due to increased intracranial pressure This young girl suffered from typical recurrent angioneurotic edema, characterized by involvement of the nose chin, eyelids and extremities ever since the onset of menstruation Oddly enough, during an attack involving the right side of her face papilledema of the right nervehead occurred, the following day the left side of her face became edematous, with involvement of the left optic nerve Albracht s observation that the retinal vessels were normal despite the papilledema would appear to be in line with an exudative allergic reaction rather than due to increased intracranial pressure

Retrobulbar Neuritis

Retrobulbar neuritis is a form of optic neuritis which occurs somewhere along the optic nerve, usually the disk is apparently unaffected when examined with the ophthalmoscope The etiology of the condition has interested both ophthalmologists and neurologists The most common cause of this type of optic nerve involvement is multiple sclerosis (24) but there are nevertheless, a large number of patients with this disease who do not develop multiple sclerosis A host of other etiologic factors have been implicated, such as extension of infection from the sinuses vitamin deficiency, encephalomyelitis and arteriosclerosis Allergy is probably one of the factors in this group and several case reports in the literature bear out this assumption

Since allergic phenomena can cause papillitis, it is not surprising that optic neuritis occurring posterior to the nervehead may have an allergic basis Atopic reactions in general are often self limited and resorb relatively quickly after a limited exposure Retrobulbar neuritis is also a self-limited disease which improves within a varying period of time and leaves behind relatively few sequelae—unless it recurs often

It is possible that the basic pathology in allergic retrobulbar neuritis is edema of the optic nerve somewhere behind the papilla or a temporary vascular lesion in the optic nerve

Kennedy (4) has recorded several instances in which he believes that retrobulbar neuritis was the result of allergy A physician who was subject

to eczema suffered from retrobulbar neuritis first in one eye and then the other He also suffered from a sharp cerebellar seizure and at another time from right hemiplegia with an abnormal plantar reflex and severe imbalance on the right side of the body All of these neurologic disorders were probably allergic in origin One cerebellar attack occurred according to the patient after inadvertently crossing the pork line

Another patient was a twenty eight year old man who was subject to swellings of various sizes for a period of five years These were occasionally superficial but usually deep seated in the muscles Two years after their inception and during the course of an attack he had a dull headache and lights appeared foggy and prismatic In a few hours he could no longer see with his right eye and the globe was acutely tender and surrounded with an area of pain A year later vision in the right eye was lost but was regained within two weeks This patient also had suffered from asthma as a child and his mother had an attack of urticaria after eating fish Although Kennedy does not offer a diagnosis in this case we feel that the patient probably suffered a bout of retrobulbar neuritis No pathologic findings are mentioned other than that there was an opacity in the left vitreous

In his discussion of Kennedy's paper Frantz (25) reported an informative example A sixteen year old girl was allergic to chocolate and eggs but she had had no attacks for several years because she had abstained from eating chocolate In March 1937 she secretly started to eat chocolate again During the following eight months she suffered from four attacks with various neurologic signs and symptoms such as numbness incoordination of extremities exaggerated deep reflexes and diminution of pain and temperature on one side of the body In the midst of the last attack she developed typical retrobulbar neuritis With the elimination of allergenic foods large amounts of magnesium sulfate by mouth and fifty cubic centimeters of fifty per cent glucose intravenously the patient recovered

Another interesting case of retrobulbar neuritis is that described by Allen and Seidelman (26) in a sixty three year old woman She was subject to many allergies and especially to hives caused by strawberries and tomatoes Since 1939 the patient had had recurrent attacks of slight fogginess of vision in either eye but more frequently in the left eye In 1947 she suffered from severe pain in the left eye and soreness on the left side of her scalp Although vision in both eyes could be corrected to 20/30 the left eye revealed absolute paracentral scotomas for red and relative one for green and the right eye had a relative paracentral scotoma for red Skin tests showed positive reactions to bananas camel and cat dander Within a short time of ingestion of Pyribenzamine and avoidance of allergens the patient's vision improved

Reaction to cold It is interesting to not[...]
[...]s gives allergi[...]

[...]with cold occasion
[...]group of physical
[...]cold lake, one [...]t one described by Wilder [...] catarrh Probably
[...]emporary blindness On contact with cold one of his patients developed urticaria prurigo and
[...]r symptoms While Wilder (27) After
[...]ossible that this patient had attacks of [...] does not interpret the ocular findings it is
[...]tter explanation [...] cold on other occasions he had simi[...]
[...]robulbar neuritis However [...]
[...]xposure to cold caused spasm
[...]blindness

[M]ICROBIALLERGIC REACTIONS OF THE RETINA

Although microbial allergy of the optic nerve and retina is rarer than the atopic and anaphylactic varieties at least one case that of Weizenblatt (28), is particularly convincing This author observed an eighteen year old boy who had received an intracutaneous injection of one tenth of a cubic [c]entimeter of old tuberculin (U S P) which had resulted in a marked cu[t]aneous reaction Five days later this patient developed bilateral neuro[re]tinitis and cyclitis The disk was hyperemic and covered with exudate [T]here was edema of the retina including the macula hemorrhages in the periphery of the fundus and sheathing of the large vessels The vision was 20/200 in the right eye and 20/100 in the left It returned to almost 20/20 [i]n four to five months Six and a half years later the same patient had another skin test with old tuberculin The skin reaction though fairly marked was not as great as the original one six years previously Seven days thereafter, however bilateral neuroretinitis and cyclitis developed The picture was similar to that of the previous attack Both times the [p]atient had a moderate blood eosinophilia Weizenblatt makes the ob[s]ervation that the first tuberculin test with stronger cutaneous reaction [ga]ve a greater degree of ocular complication than the second skin test with [le]ss reaction

Muncaster and Allen (29) had previously described the case history of a [sc]hool teacher who had decided to take the tuberculin test while her stu[]dents were being screened The first test dose gave a negative reaction Two weeks later she received another injection of 0 005 mg of purified protein derivative of tuberculin The second dose gave her a general reac[]tion with fever and malaise Ocular signs and symptoms occurred a few days later and included bilateral iridocyclitis and retinal periarteritis Within three months the eyes returned to normal More recently Miller [a]nd Smerz (30) reported bilateral posterior uveitis complicating a positive [t]uberculin cutaneous reaction However they did not mention any retinal [o]r optic nerve involvement

Another microbiallergic fundus lesion is mentioned by Kennedy (5) who cites the case of an English girl who was subject to attacks of uniocular loss of vision of varying degree lasting three to four days She suffered from recurrent attacks of eczema and developed asthmatic attacks when exposed to rabbits Her tonsils were infected with *Streptococcus viridans* She was intensely sensitive to toxins of this bacterium Following the removal of her tonsils and the enhancement of her immunity to this organism four years passed without an attack

Retrobulbar neuritis has been reported following prophylactic vaccination against rabies (31) Trypanosomiasis may cause fibrinous perivascular exudates in the retina and prepapillary exudates in the vitreous Habig (32) considers these to be on an allergic basis Papilledema however, is secondary to cerebral involvement

OTHER REACTIONS OF POSSIBLE ALLERGIC ORIGIN

An allergic etiology may be considered in certain lesions of the retina and optic nerve if they occur in allergic individuals or if certain facets of the ocular disorder offer clues to such a causation. Chief among these lesions are choroidal and retinal periarteritis nodosa and central angiospastic retinopathy The occurrence of retinal detachment on an allergic basis is open to grave doubt but deserves some discussion

Choroidal and Retinal Periarteritis Nodosa

Periarteritis nodosa is included among the allergic diseases because there is very good evidence that it is probably allergic in nature However, thi ... cumstantial information ev ... than women in a ratio of 4 to 1 It is a chronic disease characterized by a low grade septic temperature curve emaciation and anemia The symptomatology is bizarre because the necrotizing process characteristic of the disease may affect the arteries of one set of organs followed apparently by a subsidence of symptoms and then affect the arterial system of another set of organs Thus there are numerous exacerbations and remissions The kidney is often involved with albuminuria and increase in nonprotein nitrogen and there is an increase in blood pressure

The most common ocular finding in periarteritis nodosa is a hypertensive (albuminuric) retinopathy (33) or a hemorrhagic neuroretinitis with retinitic patches (34) This retinal condition is not due to focal periarteritis nodosa in the eyes but is a result of the extensive generalized effects of the disease on the kidney and the circulatory system (33 34) Less frequently there is fundus evidence of local periarteritis nodosa The

foci appear in the periphery of the fundus as grayish white in color, but with blurred margins, over a period of time they change into well defined yellowish white and sharply defined black spots These are the choroiditic foci of periarteritis nodosa The rarest type of involvement is that of the retinal vessels themselves Typical retinal periarteritis nodule formation had been noted only four times in pathologically prepared specimens among three hundred and fifty reports in the literature reviewed by Goldsmith (34) However, from a practical point of view it is extremely difficult to diagnose such retinal nodules, clinically, in the presence of hypertensive retinopathy The choroiditic foci, however, can be recognized with an ophthalmoscope if retinopathy is not too extensive In Goldsmith's case there was, in addition to angiospastic changes, a fusiform swelling of the inferior temporal artery

Several cases have been reported with generalized periarteritis nodosa and retinal detachment (35–39) Since histologic examination could not be performed in any of these cases at the time of the detachment, Boeck makes the observation that it is impossible to definitely know whether or not this detachment is caused by local periarteritis nodosa of the choroidal vessels with subsequent exudative detachment of the retina In some of the cases, when the retina became spontaneously reattached, both undefined white spots and clearly white and pigmented circumscribed areas have been observed resembling choroiditic foci It is the consensus that an exudative detachment is caused by extensive periarteritis of the choroidal vessels It is also possible that the detachment in some cases may be due to hypertensive retinopathy In the latter instance one would not expect spontaneous reattachment It is interesting to note that we have observed retinal detachment in another collagen disease namely lupus erythematosus and also in conjunction with atopic cataracts

The chief pathologic findings consist of an inflammatory process beginning in the periphery of the medium and small arteries with a predilection for the media where extensive fibrinoid degeneration occurs The intima is also involved secondarily Thus the primary necrotizing lesion occurs in the arteries There is extensive vascular and perivascular infiltration by polymorphonuclear leukocytes, eosinophiles and to a lesser extent, lymphocytes The smaller vessels become thrombosed, especially as a result of involvement of the intima, and the neutrophiles become replaced by lymphocytes

The fibrinoid degeneration consists of a pathologic change of the collagen of the vessel wall, and usually involves chiefly the media but occasionally extends through the entire vessel wall Finally, as a result of the changes described some of the arteries become transformed into granulomas consisting of fibroblasts and histiocytes with some round cells The changes in

the choroid are similar to those elsewhere in the body. The tissues in the areas surrounding the diseased arteries may show proliferation of the pigment epithelium in some places and degeneration of this epithelium in others. More rarely the blood vessels of the retina are affected with a similar process. Herrenschwand (40) reported a case with involvement of the central retinal artery. *Of course the retinal lesions due to hyper*tensive retinopathy occurring in patients with periarteritis nodosa have no distinguishing characteristics.

In reporting a pathologically confirmed instance of what the authors consider to be allergic granulomatous ocular angiitis with uveoscleritis and papilledema, Cury, Breakey, and Payne (41) *utilized the interesting* classification of Zeek (42) and Churg and Strauss (43). These authors divide periarteritis nodosa into 1) polyarteritis, a necrotizing inflammatory disease *of the muscular type arteries*; 2) hypersensitivity angiitis related to drug allergy; and 3) allergic granulomatous angiitis associated with asthma and possibly other atopic manifestations.

Since ocular periarteritis nodosa is part of a generalized medical disorder, the treatment is usually directed by the internist. Corticosteroids *and ACTH are the most effective agents available at present against this* disease.

Evidence for allergic etiology of periarteritis nodosa. Klemperer, Pollack, and Baehr (44) have shown that the chief lesion in periarteritis nodosa is an alteration of the collagen of the blood vessels and have placed it among the collagen diseases. Gruber (45, 46) has called attention to the fact that the histologic picture of the allergic reaction described by Roessle bears a striking resemblance to the pathology of periarteritis nodosa. *Finally, Rich and Gregory (47, 48) were able to induce experimentally* similar changes in the blood vessels as a result of allergic reactions to drugs, especially sulfonamides. They believed that the continued administration of sulfonamides after a hypersensitive reaction has occurred may increase the danger of vascular damage by prolonging the contact of the sensitized body with the offending antigen. Numerous cases have apparently occurred secondary to sulfonamide sensitivity.

Other etiologic factors have been indicted, and among the more probable is that the *disease is due to a virus*. Boeck (33) suggests that this virus may be closely related to herpes zoster. It is impossible at present to conclusively state which causative factor is the correct one. We *feel at pres*ent that there is greater evidence in favor of an *allergic than a viral* etiology.

Central Angiospastic Retinopathy

all

athy has certain features which link it to allergy Wolkowicz (49) points out the fact that the lesion in this disease resembles the urticarial wheal and was prompted to perform certain laboratory experiments on rabbits to prove an allergic etiology

The chief clinical signs and symptoms of central angiospastic retinopathy can be summarized as follows (50) 1) There is a sudden diminishing of vision The patient may report a veil or spot before the affected eye Often he notices minification of objects 2) Although the patient complains of disturbances in vision the acuity as measured with the Snellen chart may be the same as before the episode or there may be a loss of only one or two lines on the chart 3) The disease is usually unilateral although rarely bilateral cases do occur 4) Findings may be negative with ordinary ophthalmoscopic methods but with red free light minimal hemorrhages and macular edema may be noted In more severe cases the macular edema is readily visible with the ophthalmoscope and it may appear as a flat well circumscribed macular detachment For this reason Walsh and Sloan (51) called this condition idiopathic flat detachment of the retina

Priestly and Force (52) have designed a new entoscope which utilizes Scheerer's phenomenon to render visible the red blood cells circulating in the paramacular region In this way the macular circulation of the affected eye can be compared with the normal one In this instrument the patient looks into a metal box containing a mercury vapor grid and a diffusing screen The light is seen through one of two openings and as the patient begins to look into the lighted field he sees the flying corpuscles The average normal eye sees about twenty to thirty light corpuscles which appear suddenly at the margin of the field or any place in the field with a sudden jerk Abnormal responses include seeing fewer cells in one eye than the other corpuscles in uniform motion (as compared with the jerky movement in normal eyes) or decreased cells in one sector Finally if the lesion is extensive enough the patient may report no cells In patients with central angiospastic retinopathy especially with meager ophthalmoscopic signs such abnormal reactions to Scheerer's phenomenon are very helpful in confirming the diagnosis

Most patients recover completely but a number remain with permanent visual damage and permanent pigmentary changes in the choroid may occasionally persist Recurrent attacks occur in about half of the cases Although spontaneous recovery is the rule systemic vasodilators are the treatment of choice and probably accelerate recovery When the lesions do not disappear systemic corticosteroid therapy may be utilized but we have not had much success with such treatment in such persistent cases Patients with this condition are usually forbidden to smoke because of the vasospasm induced by nicotine

Evidence for allergic etiology of central angiospastic retinopathy When

Horniker (53) described central angiospastic retinopathy in 1927 and reported seventeen cases with this condition he stressed the fact that this disease is similar to intermittent claudication bronchial asthma urticaria migraine vasomotor rhinitis erythema and eczemas in that there is a basic vasoneurosis or vasomotor instability In many allergic disorders such phenomena occur Lowenstein (54) was apparently the first to consider allergy as an etiologic factor in this disease Bothman (6) supported this view and described cases with transient macular edema occurring during allergic attacks elsewhere in the body Duggan (55) and Berens Sayad and Girard (56) similarly felt that allergy was the chief etiologic factor Klien (57) also mentions allergy as a possible factor in addition to several others such as infections toxins and metabolic or endocrine dysfunctions

Wolkowicz (49) attempted to prove experimentally the hypothesis favoring allergic etiology He felt that the lesion resembles a nonspecific focal allergic reaction and attempted by two different approaches to provoke a localized retinal allergic reaction

In the first procedure he injected into the suprachoroidal space of a rabbit's eye 0 01 cc of horse serum The following day the bleb was flattened and two or three days later the fundus was ophthalmoscopically normal Two weeks later 1 0 cc of horse serum was injected intravenously In some cases there was no response In favorable animals a faint aqueous flare vitreous haze temporary dilatation of vessels and focal retinal edema occurred This would clear spontaneously in ten days In other rabbits the intravenous horse serum was shocking enough to kill the animal

The second technique utilized two cubic centimeters of one per cent eosin solution intravenously to sensitize the rabbit The eye was exposed to carbon arc light seven days later for two minutes using a zircon arc photomicrographic lamp The area of edema obtained in the rabbits retina by this method resembles that of central serous retinopathy Each wheal was well outlined purplish red and elevated to seven or eight diopters The surrounding retina was normal

The similarity of these lesions to central angiospastic retinopathy in humans is suggestive that the latter has a similar allergic etiology The vascular spasm resulting from horse serum sensitivity produced a scattered predominantly choroidal response the second method utilizing photosensitivity caused a localized retinal vascular reaction These experiments are suggestive and a step in the right direction However a great deal more evidence will have to be accumulated before we can definitely consider central serous retinopathy to be an allergic reaction

Braley and Hamilton (57a) have called attention to central serous

choroiditis associated with amebiasis. In such patients the lesions are aggravated by steroids and respond to specific antiamebic therapy. Since amebic choroiditis resembles central angiospastic retinopathy, especially early in the disease, it is therefore important to investigate all patients with macular lesions of obscure etiology for evidence of amebiasis.

Retinal Detachment

In view of the recent research on retinal detachment and the newer methods of studying the relationship of the retina to the vitreous, it is highly questionable whether allergy plays any significant role in the pathogenesis of the disease. Present-day thought would indicate that mechanical factors, especially traction on the retina by vitreous adhesions or bands, are most important etiologically.

We use the term retinal detachment in this discussion in its usual sense, that is, typical detachment with retinal breaks or disinsertions. We are not referring to exudative processes resulting in permanent or transitory detachments such as occur in inflammatory processes. It is conceivable that allergic inflammation may lead to this; however, atopic reactions in general are not severe enough to do so. It is also possible that mechanical factors induced by allergies, such as intense sneezing, may precipitate typical detachments in susceptible patients. It must be stressed, as was developed in chapter 20, that there is an unusually high incidence of retinal detachment in patients with cataracts complicating atopic dermatitis. The reasons for this are obscure. As previously discussed in this chapter, retinal detachment is also occasionally observed in patients with periarteritis nodosa.

Only a few observations linking allergy to retinal detachment are available. Considering the large number of allergic individuals and the not infrequent occurrence of detachment of the retina in ophthalmic practice, it would appear that if allergy were a definite factor in its pathogenesis many more cases would be reported. However, a very provocative and interesting experimental study by Godtfredsen (58) on the relationship between allergy and retinal detachment suggests that the idea cannot be entirely dismissed.

According to this author, in all cases of detachment with tears of the retina, the subretinal fluid contains a considerable amount of hyaluronic [illegible]

of the sequence of events in retinal detachment. According to him, the primary retinal lesion is vascular, and results in the development of local ischemia. This leads to tissue necrosis and cystoid degeneration. These

cysts finally rupture With all of this cellular activity hyaluronidase is liberated This enzyme in turn depolymerizes the hyaluronic acid in the adjacent vitreous body and thus reduces its viscosity thus enabling the new liquid vitreous to pass through the retinal tears When there is a balance between the amount of fluid vitreous in front of the detached retina and behind it, the depolymerization of the hyaluronic acid will stop Thus there is a higher concentration of hyaluronic acid in the subretinal fluid in cases of long-standing detachment

The relationship between hyaluronic acid and the allergic state lies in the fact that hyaluronidase may become inactivated by antihistamines Since hyaluronidase is liberated by allergic vascular reactions as shown by Mayer and Kull (59) it is reasonable (according to Godtfriedsen) to suppose that an analogous angioneurotic vascular lesion occurring in some part of the peripheral retina may result in a similar liberation of hyaluronidase

Of some practical importance is Godtfriedsen's suggestion that tests indicating little or no hyaluronic acid in the subretinal fluid may help differentiate cases of malignant melanoma from idiopathic retinal detachment Another point of interest is that the concentration of hyaluronic acid present may furnish a clue as to the duration of the detachment The older the process the higher the concentration Godtfriedsen recommends supplementary treatment of detachments by antihistaminics in order to inactivate the hyaluronidase to prevent further vitreous liquefaction

Prewitt (60) described a case of bilateral detachment in an individual with a highly allergic background This patient had blurred vision following *the development of nodular swellings all over her body The fundus itself* had a corrugated appearance following an intracapsular lens extraction This subsided, but the retinal edema returned three months later and was followed in several months by a retinal detachment Prewitt suggested that there may have been nodular swellings behind the retina and that *these caused the detachment*

Balyeat (61) reported bilateral retinal detachment in a patient twenty one years of age who suffered from asthma hay fever vasomotor rhinitis and eczema aggravated by contact with silk cloth *Since the retina is* primarily an ectodermal structure he suggests that retinal detachment may occur in a manner similar to involvement of the skin or olfactory epithe-

* retinal tears Wiener (62)
use of retinal detachment,
observed such a case He

did mention however a suggestive case in which a patient with chronic skin disease developed a flat detachment of the retina This patient was sensitive to trichophytin He suggested that the focal reaction *in the retina*

was similar to the focal reaction in the skin The possibility of atopic dermatitis in this patient does not seem to have been considered

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